PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/44, C07D 491/107

A1

(11) International Publication Number: WO 98/36749

(43) International Publication Date: 27 August 1998 (27.08.98)

(21) International Application Number: PCT/US98/02338

(22) International Filing Date: 7 February 1998 (07.02.98)

(30) Priority Data:
60/038,917 21 February 1997 (21.02.97) US

(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventors: AHMAD, Saleem; 2094 Ohadi Drive, Wall, NJ 07719 (US). STEIN, Philip, D.; 3 Harbourton Ridge Drive, Pennington, NJ 08534 (US). FERRARA, Francis, N.; 1745 Arrowbrook Drive, Martinsville, NJ 08836 (US). ATWAL, Kamail, S.; 92 Valley View Way, Newton, PA 18940 (US).

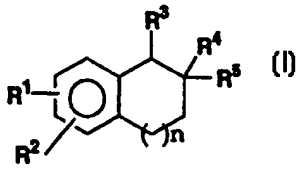
(74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*

(54) Title: TETRALONE DERIVATIVES AS ANTIARRHYTHMIC AGENTS

(57) Abstract



(I)

Tetralone derivatives of formula (I) where $R^1$ is halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, (aryl)alkenyl, (aryl)alkynyl, alkoxy, O-alkenyl, O-aryl, O-alkyl(heterocyclo), COO-alkyl, alkanoyl, CO-amino, CO-substituted amino, alkyl-CO-amino, alkyl-CO-substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-alkyl(heterocyclo), N(alkyl)CO-alkyl, N(alkyl)CO-aryl, N(alkyl)CO-heterocyclo, N(alkyl)CO-alkyl(heterocyclo); $R^2$ is hydrogen, alkyl, halo, aryl, alkoxy, amino, substituted amino; $R^3$ is oxo, hydroxy, alkoxy, O-COalkyl, -O-COaryl, -O-COheterocyclo, NOH, NO-alkyl, N-amino, N-substituted amino, N-NHCONHalkyl, N-NHSO$_2$alkyl, N-NHSO$_2$aryl, amino, substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-heterocyclo, spiroheterocyclo; $R^4$ is hydrogen, alkyl, alkyl(COalkyl), alkyl(COOalkyl); or $R^3$ and $R^4$ taken together with the atoms to which they are attached form a five- to seven-membered ring which can contain up to three heteroatoms selected from oxygen, nitrogen and sulfur; $R^5$ is hydrogen, alkyl, alkenyl, alkyl(heterocyclo), alkyl-NHCO(alkyl), alkyl-NHCO(aryl), alkyl-NHCO(heterocyclo), alkyl-NHCO(alkylheterocyclo); and n is an integer of 0 to 2. These compounds have been found to be useful in the treatment of arrhythmia.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

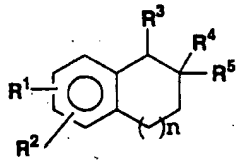
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# TETRALONE DERIVATIVES AS ANTIARRHYTHMIC AGENTS

## Brief Description of the Invention

This invention is concerned with compounds of the formula

I



where

$R^1$ is halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, (aryl)alkenyl, (aryl)alkynyl, alkoxy, O-alkenyl, O-aryl, O-alkyl(heterocyclo), COO-alkyl,alkanoyl, CO-amino, CO-substituted amino, alkyl-CO-amino, alkyl-CO-substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-alkyl(heterocyclo), N(alkyl)CO-alkyl, N(alkyl)CO-aryl, N(alkyl)CO-heterocyclo, N(alkyl)CO-alkyl(heterocyclo);

$R^2$ is hydrogen, alkyl, halo, aryl, alkoxy, amino, substituted amino;

$R^3$ is oxo, hydroxy, alkoxy, O-COalkyl, -O-COaryl, -O-COheterocyclo, NOH, NO-alkyl, N-amino, N-substituted amino, N-NHCONHalkyl, N-$NHSO_2$alkyl, N-$NHSO_2$aryl, amino, substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-heterocyclo, spiroheterocyclo;

$R^4$ is hydrogen, alkyl, alkyl(COalkyl), alkyl(COOalkyl); or

$R^3$ and $R^4$ taken together with the atoms to which they are attached form a five- to seven-membered ring which can contain up to three hetero atoms selected from oxygen, nitrogen and sulfur;

$R^5$ is hydrogen, alkyl, alkenyl, alkyl(heterocyclo, alkyl-NHCO(alkyl), alkyl-NHCO(aryl), alkyl-NHCO(heterocyclo), alkyl-NHCO(alkylheterocyclo); and

n is an integer of 0 to 2.

These compounds are useful in the treatment of arrhythmia. The invention is also concerned with pharmaceutical compositions comprising one or more of the novel compounds as an active antiarrhythmic agent either alone or in combination with other cardiovascular agents such as a B-blocker or other antiarrhythmic agent; and a method of treating arrhythmia by administration of one of the novel compounds or compositions thereof to a patient in need of such treatment.

## Detailed Description of the Invention

### Definition of Terms

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The term "alkyl" refers to both straight and branched chain groups having 1 to 8 carbon atoms, preferably 1 to 5 carbons, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, the various branched chain isomers thereof, such as isopropyl, t-butyl, isobutyl, isohexyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl and the like; as well as such groups substituted by, one or more substituents such as halo, alkoxy, amino, substituted amino, aryl, cycloalkyl, hydroxy, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, alkylthio and the like.

The term "alkoxy" refers to alkyl-O-.

The term "alkylthio" refers alkyl-S-.

The term "alkenyl" refers to any of the above alkyl groups further containing at least one carbon to carbon double bond.

The term "alkynyl" refers to any of the above alkyl groups further containing at least one carbon to carbon triple bond.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "cycloalkyl" refers to saturated cyclic hydrocarbon groups containing 3 to 8 ring carbons optionally substitued with one or more substituents such as alkyl or hydroxy.

The term "halogen" or "halo" refers to chlorine, bromine, iodine and fluorine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, 1-naphthyl, 2-naphthyl, phenanthrene or dihydrophenanthrene; or such groups substituted with one or more substituents such as alkyl, alkylthio, alkoxy, halo, nitro, cyano, hydroxy, amino, substituted amino, phenyl, -C(O)-phenyl, substituted phenyl, -C(O)-substituted amino, heterocycle, carboxylic acid or carboxylic ester.

The term "aryl" also includes those groups listed above fused to a five- or six-membered ring which optionally contains an oxygen, sulfur or nitrogen atom. The five- or six-membered ring may further optionally be substituted with for example, alkyl or -phenyl-$CF_3$.

The term "heterocyclo" or "hetero" refers to fully saturated or unsaturated rings of five or six atoms containing one or two oxygen and/or sulfur atoms and/or one to four nitrogen atoms provided that the total number of hetero atoms in the ring is four or less. Exemplary monocyclic heterocyclo groups include 2- and 3-thienyl, 2- and 3-furyl, 2-, 3- and 4-pyridyl and imidazolyl.

The term heterocyclo or hetero also includes bicyclic rings wherein the five- or six-membered ring containing oxygen and/or sulfur and/or nitrogen atoms as defined above is fused to a benzene ring and the bicyclic ring is attached by way of an available atom.

Exemplary bicyclic hetero groups include 4-, 5-, 6- or 7-indolyl, 4-, 5-, 6- or 7-isoindolyl, 5-, 6- , 7- or 8-quinolinyl, 5-, 6-, 7- or 8-isoquinolinyl, 4-, 5-, 6- or 7-benzothiazolyl, 4-, 5-, 6- or 7-benzoxazolyl, 4-, 5-, 6- or 7-benzimidazolyl, 4-, 5-, 6- or 7-benzoxadiazolyl and 4-, 5-, 6- or 7-benzofuranzanyl.

The term heterocyclo or hetero also includes such monocyclic and bicyclic rings wherein an available atom is substituted by one or more substituents such as alkyl, aryl, alkylthio, alkoxy, halo, nitro, keto, cyano, hydroxy, azo, oxo, thiazo, amino, substituted amino, carboxylic acid, carboxylic ester, or alkoxy further substituted with a carboxylic acid or a five- to eight-membered ring optionally containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur, optionally substituted by groups such as alkyl or halogen.

The term "substituted amino" refers to a group of the formula $-NZ^2Z^3$ wherein $Z^2$ is hydrogen, alkyl, cycloalkyl, aryl, morpholinylalkyl, heterocyclo or (heterocyclo)alkyl and $Z^3$ is hydrogen, alkyl, cycloalkyl or aryl further substituted with a carboxylic acid or carboxylic ester, provided that when $Z^2$ is hydrogen, then $Z^3$ is other than hydrogen; or $Z^2$ and $Z^3$ taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, aryl or hydroxy.

Throughout the specification, groups and substituents thereof are chosen to provide stable moieties and compounds.

The compounds of formula I form salts which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention.

The compounds of formula I may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts may be obtained, for example, by exchanging the carboxylic acid protons, if they contain a carboxylic

acid, in compound I with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by evaporation. Other salts can be formed as known to those having ordinary skill in the art.

The compounds of formula I may form salts with a variety of organic and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts may be formed by reacting compound I in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

In addition, zwitterions ("inner salts") may be formed.

A compound of the formula I may also have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985);

b) *Methods in Enzymology*, Vol. 42, 309-396, edited by K. Widder et al. (Academic Press, 1985);

c) *A Textbook of Drug Design and Development*, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, 113-191 (1991);

d) *Advanced Drug Delivery Reviews*, H. Bundgaard, 8, 1-38 (1992);

e) *Journal of Pharmaceutical Sciences*, H. Bundgaard et al., 77, 285 (1988); and

f) *Chem Pharm Bull*, N. Kakeya et al., 32, 692 (1984).

It should further be understood that solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in diastereomeric forms or in mixtures thereof. The below described processes can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

**Use and Utility**

The compounds of formula I are useful in the treatment of arrhythmia. More specifically, the compounds of the present invention have the pharmacological properties required for the antiarrhythmic agents of Class III.

Class III agents increase myocardial refractoriness via a prolongation of cardiac action potential duration. Theoretically, prolongation of the cardiac action potential can be achieved by enhancing inward currents (i.e. $Na^+$ or $Ca^{2+}$ currents; hereinafter $I_{Na}$ and $I_{Ca}$ respectively) or by reducing outward repolarizing potassium ($K^+$) currents. The delayed rectifier ($I_K$)$K^+$ current is the main outward current involved in the overall repolarization process during the action potential plateau, whereas the transient outward ($I_{to}$) and inward rectifier ($I_{K1}$)$K^+$ current are responsible for the rapid initial and terminal phases of repolarization, respectively. Cellular electrophysiologic studies have demonstrated that $I_K$ consists of two pharmacologically and kinetically distinct $K^+$ current subtypes, $I_{Kr}$ (rapidly activating and deactivating) and $I_{Ks}$ (slowly activating and deactivating).

Most Class III agents that are known to be in development predominantly block $I_{Kr}$. These agents have a potential liability in that they have an enhanced risk of proarrhythmia at slow heart rates. The

compounds of the present invention prolong the mycocardial action potential in vitro without a significant depression of the Vmax and with the prolongation of Qtc-interval in anesthetized dogs. In addition the compounds of the present invention selectively block $I_{Ks}$. The preferred compounds of the present invention are those which have selectivity of $I_{Ks}$:$I_{Kr}$ greater than or equal to 5.

The compounds of the present invention are effective in treating and preventing all types of arrhythmias including ventricular and atrial (supraventricular) arrhythmias. The compounds of the present invention are especially useful to control reentrant arrhythmias and prevent sudden death due to the ventricular fibrillation.

In the novel method of this invention of treating arrhythmia, a novel compound or pharmaceutically acceptable salt thereof, is administered in an amount ranging from about 0.0001 to about 20 mg per kg of body weight per day, preferably from about .001 to about 10 mg per kg of body weight per day in a single dose or in 2 to 4 divided doses.

The novel compounds of this invention can be administered as the sole active ingredient or in combination with other antiarrhythmic agents or other cardiovascular agents.

The compounds, or pharmaceutically acceptable salts thereof, of the present invention, in the described dosages, are administered orally, intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. They are preferably administered orally, for example in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum, or the like prepared by art recognized procedures. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

**Preferred Moieties**

The preferred compounds of the present invention are those compounds of formula I where:

$R^1$ is O-alkyl(aryl), CONH-alkyl, CONH-alkyl(aryl), CONH-alkyl(cycloalkyl);

$R^2$ is hydrogen;

$R^3$ is oxo, hydroxy, alkoxy or NOH;

$R^4$ is hydrogen or alkyl;

$R^5$ is alkyl, alkyl(substituted amino); and

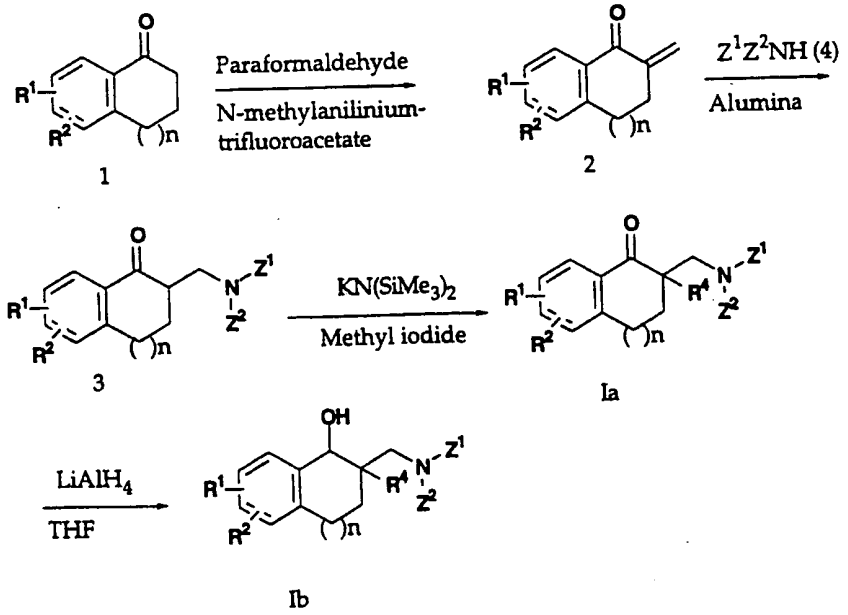
n is an integer of 0 to 2.

**Process of Preparation**

The compounds of the instant invention be obtained by methods exemplified by the following descriptions.

Compounds of formula Ia (which are compounds of formula I where $R^3$ is oxo and $R^5$ is is alkyl(substituted amino)) and Ib (which are compounds of formula I where $R^3$ is hydroxy and $R^5$ is alkyl(substituted amino)) can be prepared according to Scheme 1.

**Scheme 1**

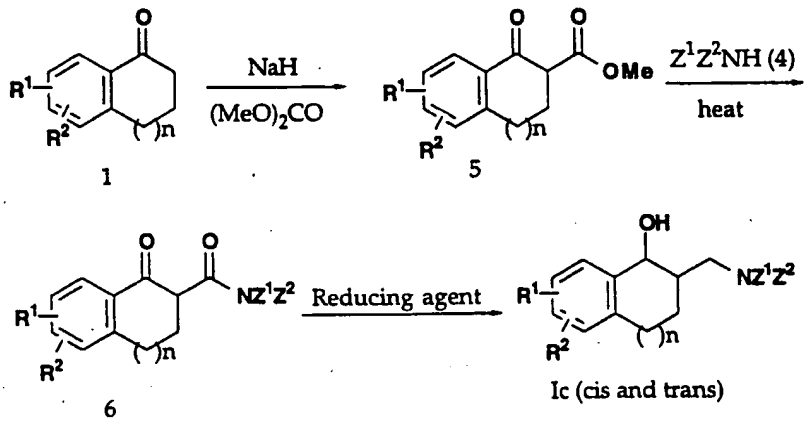


The ketone of formula 1 is reacted with paraformaldehyde in the presence of N-methylanilinium trifluoroacetate to yield compounds of formula 2 which undergoes the Michael addition with an amine of formula 4 to provide compounds of formula 3. Compounds of formula can be alkylated ($R^4X$, base) to provide compounds of formula Ia which can be further reduced to compounds of formula Ib.

Compounds of formula 1 and 4 are commercially available or they can be prepared by modification of the methods known in the literature.

Compounds of formula Ic (which are compounds of formula I where $R^3$ is hydroxy and $R^4$ is hydrogen and $R^5$ is alkyl(substituted amino)) can be prepared according to Scheme 2.

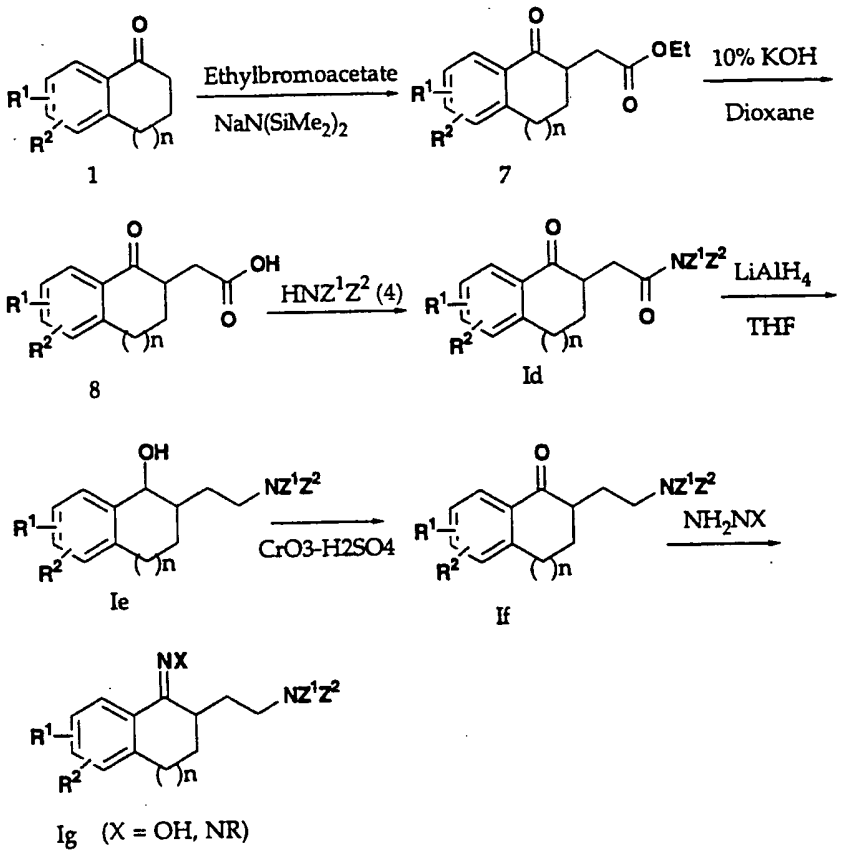
**Scheme 2**




The ketone of formula 1 is acylated with dimethylcarbonate and sodium hydride to give compounds of formula 5 which is condensed with an amine of formula 4 to provide compounds of formula 6. Reduction of 6 with a reducing agent (e.g., lithiumaluminum hydride) provides compounds of formula Ic.

Compounds of formula Id-g can be prepared according to Scheme 3.

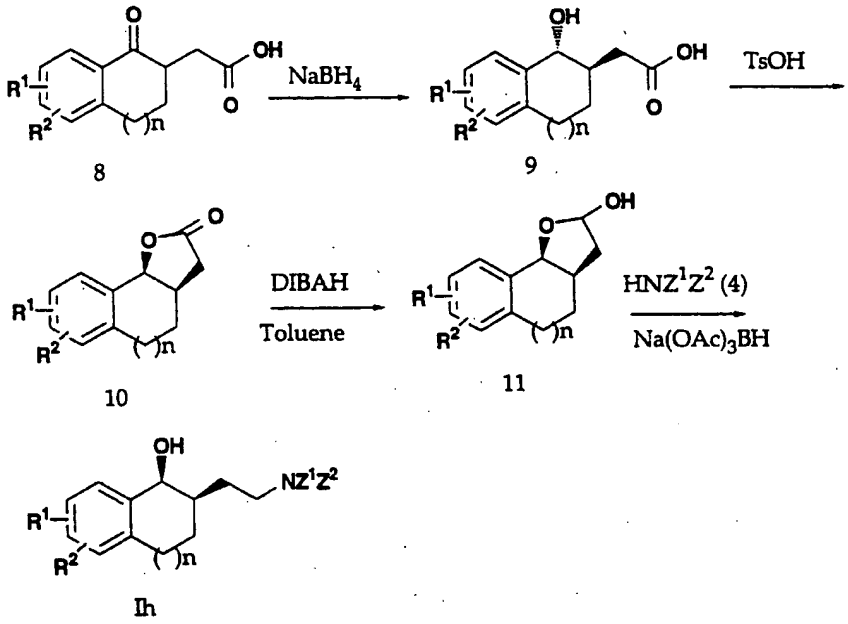
**Scheme 3**




The ketone of formula 1 is alkylated with methyl bromoacetate and a base to provide compounds of formula 7. The ester in 7 is saponified to give the acid of formula 8 which on coupling with an amine 4 ($Z^1Z^2NH$) provides amides of formula Id. Compounds of formula Id are reduced with lithiumaluminum hydride to yield amino alcohols of formula Ie. The oxidation of the alcohol with the Jones reagent provides compounds of formula If which can be further converted to compounds of formula Ig on treatment with hydroxyl amine and hydrazine or derivatives thereof.

Compounds of formula Ih (cis-alcohol) can be prepared from compounds of formula 1 as described in Scheme 4.

**Scheme 4**

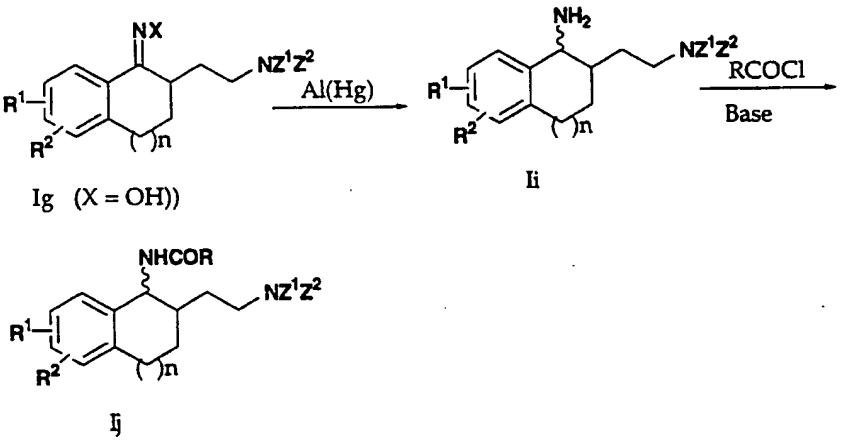



The ketone in compound 8 is reduced with sodium borohydride to give the trans-hydroxy acid of formula 9 which on treatment with an acid (e.g., p-toluenesulfonic acid) yields the cis-lactone of formula 10. The lactone in formula 10 is reduced (e.g., DIBAH) to provide the lactol of formula 11. Treatment of compound 11 with an amine of formula 4 in the presence of a reducing agent (e.g., sodium triacetoxyborohydride, sodium cyanoborohydride) provides the desired compounds of formula Ih.

Compounds of formula 8 are described in Scheme 3 and compounds of formula 4 are commercially available or they can be prepared by modification of the methods known in the literature.

Compounds of formula Ii and Ij can be prepared according to Scheme 5.

**Scheme 5**




Ig (X = OH)

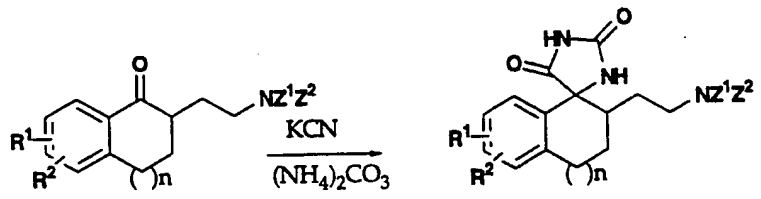
Ii

Ij

The oxime in Ig is reduced with Al(Hg) and the resulting amine Ii is derivatized with an appropriate reagent (ROCl) to provide the requisite compounds of formula Ij. Compounds of formula Ig are described in Scheme 3 and compounds of formula RCOCl are commercially available or they can be readily prepared by methods known in the literature.

The spiro heterocyclic ring containing compounds of formula Ik can be prepared from the corresponding ketones of formula If by treatment with potassium cyanide and ammonium carbonate as shown in Scheme 6.

**Scheme 6**

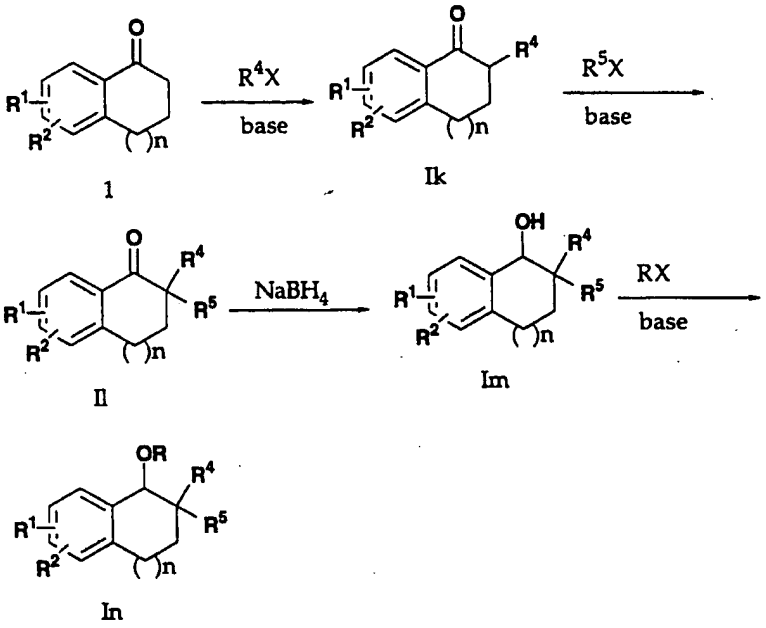



If

Ik

Compounds of formula In can be prepared as described below in Scheme 7.

**Scheme 7**

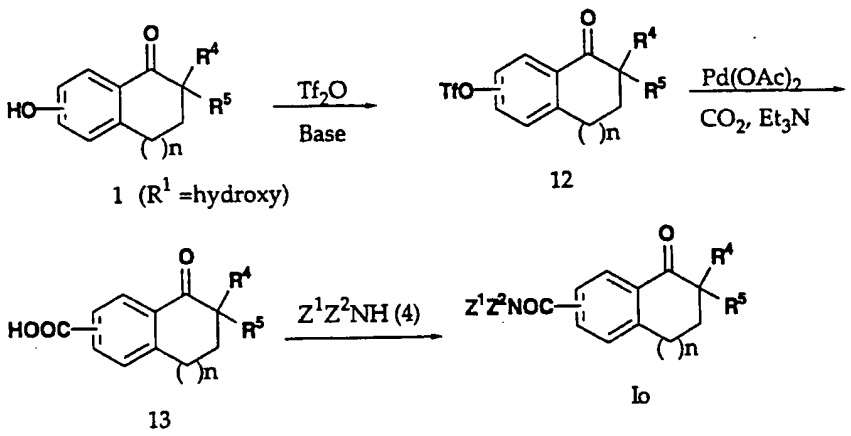



Compounds of formula Il can be prepared from compounds of formula 1 by successive alkylation with approproate alkylating agents in the presence of a base such as sodium hydride. The compounds of formula Im can be reduced with a reducing agent (e.g., sodium borohydride) to the alcohol of formula Im which can be further alkylated to provide the desired compounds of formula In.

Compounds of formula 1 are commercially available or they can be prepared by methods known in the literature. The alkylating agents of formula $R^4X$, $R^5X$ and RX are commercially available or can be readily obtained by methods known in the literature.

Compounds of formula Io wherein $R^1$ is acid or a derivative thereof can be prepared from compounds of formula 1 wherein $R^1$ is hydroxy according to Scheme 8.

**Scheme 8**




1 ($R^1$ =hydroxy) 12 13 Io

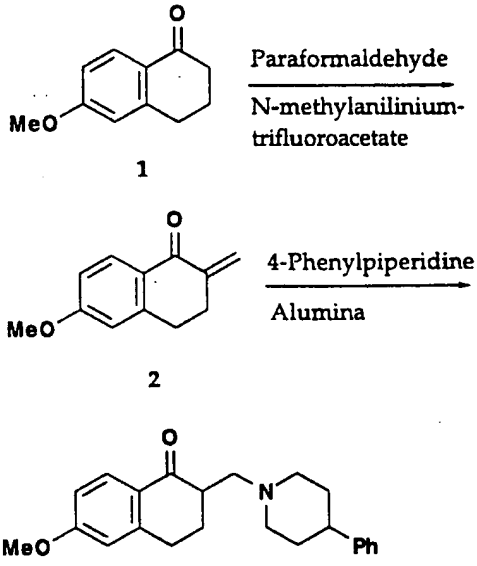
The hydroxy group in 1 is converted to a triflate 12 by treatment with triflic anhydride and a base (e.g., pyridine). The triflate in 12 can be converted to a carboxylic acid of formula 13 in the presence of a palladium catalyst. The carboxylic acid 13 can be converted to its derivatives (e.g., amide Io) by standard methods described in the literature.

**Examples**

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there many be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

## Example 1

**3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, hydrochloride**




**A. Compound 2:**

A mixture of 6-methoxytetralone (29.24 g, 165.9 mmol), paraformaldehyde (22.4 g, 746.6 mmol) and N-methylanilinium trifluoroactate (55 g, 248.9 mmol) in 250 mL THF was refluxed for 4 hours and allowed to come to room temperature. To this was added ether (250 mL) with stirring and the mixture was decanted to remove the gummy precipitate. The supernent was washed with sat. $NaHCO_3$, the oganic layer was dried ($MgSO_4$) concentrated. The residue was redissolved in ether, filtered through celite and concentrated to afford compound 2 as a thick yellow oil.

**B. 3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, hydrochloride**

To a mixture of the title A compound (2.2 g, 12.11 mmol), 4-phenylpiperidine(1.95 g, 12.11 mmol) and alumina (4.56 g) in 300 mL toluene was added water (0.219 mL) and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was then filtered, the residue washed with ethyl acetate and the combined filtrate was concentrated. The residue was dissolved in dichloromethane, acidified with 4 N HCl in dioxane, concentrated and the residue triturated sequentially with ethyl acetate and acetonitrile to afford the title compound (4.2 g, 90%) as a white solid.

mp (°C) 176-177.

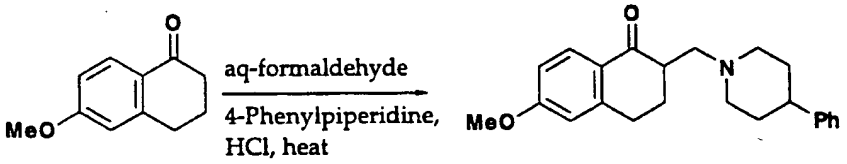
Anal. for: $C_{23}H_{27}NO_2 \bullet HCl$:

Calc'd: C, 71.58; H, 7.31; N, 3.63.

Found: C, 72.08; H, 7.21; N, 3.64.

**Example 2**

**3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, hydrochloride**



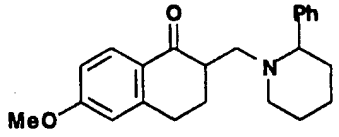

1

Concentrated hydrochloric acid (4.9 mL) was added to a solution of 4-phenylpiperidine (9.38 g, 58.2 mmol) in isopropanol (60 mL) at 10-15°C followed by the sequential addition of 6-methoxy-1-tetralone (9.76 g, 55.4 mmol), 37% aqueous formaldehyde (5.72 g) and 60 mL isopropanol. The mixture was refluxed for 1 hour, diluted with toluene, concentrated and the residue recrystallized sequentially from acetone and ethanol to afford the title compound as a white solid (5g), mp 177-8°C.

**Using methodology analogous to that described for the title compounds of Examples 1 and 2, the compounds of Examples 3 to 12 were prepared:**

**Example 3**

**3,4-Dihydro-6-methoxy-2-[(2-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

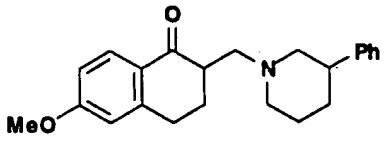



mp (°C) 110-115.

Anal. for: $C_{23}H_{27}NO_2$:

**Example 4**

**3,4-Dihydro-6-methoxy-2-[(3-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

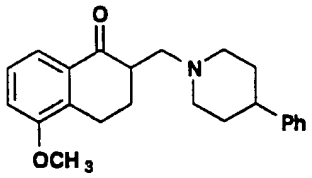



mp (°C) 75-80.

Anal. for: $C_{23}H_{27}NO_2 \cdot 1.1\ H_2O$:

**Example 5**

**3,4-Dihydro-5-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

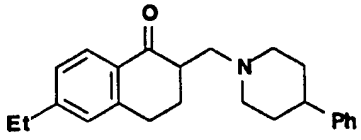



mp (°C) 186-190.

Anal. for: $C_{23}H_{27}NO_2 \bullet HCl \bullet 0.39\ H_2O$:

**Example 6**

**6-Ethyl-3,4-dihydro-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

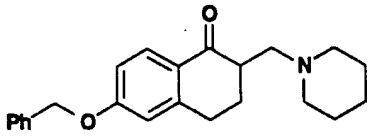



mp (°C) 177-180.

Anal. for: $C_{24}H_{29}NO \bullet HCl$:

**Example 7**

**3,4-Dihydro-6-(phenylmethoxy)-2-(1-piperidinylmethyl)-1(2H)-naphthalenone, monohydrochloride**

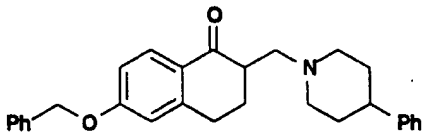



mp (°C) 189-191.

Anal. for: $C_{23}H_{27}NO_2$:

**Example 8**

**3,4-Dihydro-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 197-200.

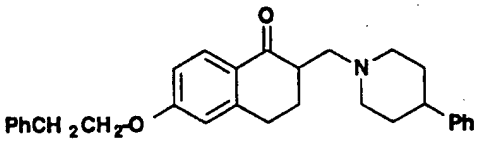
Anal. for: $C_{29}H_{31}NO_2 \bullet HCl$:

Calc'd: C, 75.38; H, 6.98; N, 3.03.

Found: C, 75.38; H, 7.03; N, 3.03.

**Example 9**

**3,4-Dihydro-6-(2-phenylethoxy)-2-(1-piperidinylmethyl)-1(2H)-naphthalenone, monohydrochloride**

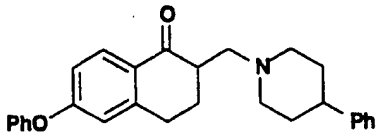


mp (°C) 78-182.

Anal. for: $C_{30}H_{33}NO_2 \bullet HCl$:

**Example 10**

**3,4-Dihydro-6-phenoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

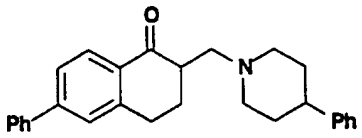


mp (°C) 183-184.

Anal. for: $C_{28}H_{29}NO_2 \bullet HCl \bullet 0.54H_2O$:

**Example 11**

**3,4-Dihydro-6-phenyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 179-180.

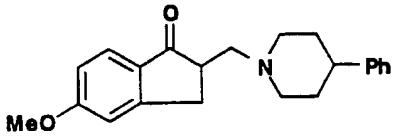
Anal. for: $C_{28}H_{29}NO \bullet HCl \bullet 0.42H_2O$:

Calc'd: C, 76.52; H, 7.07; N, 3.19.

Found: C, 76.15; H, 7.04; N, 3.56.

**Example 12**

**2,3-Dihydro-5-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1H-inden-1-one, monohydrochloride**




mp (°C) 164-166.

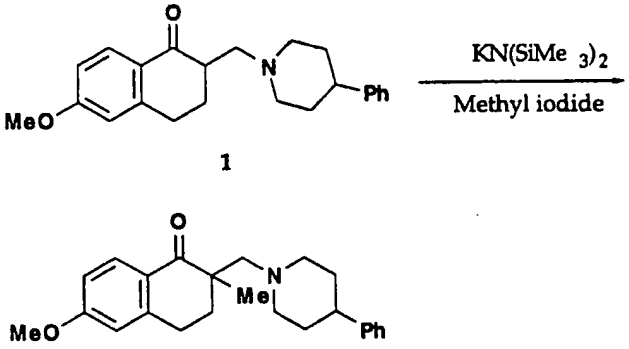
Anal. for: $C_{22}H_{25}NO_2 \bullet HCl \bullet 0.32H_2O$:

Calc'd: C, 69.95; H, 7.11; N, 3.71; Cl, 9.39.

Found: C, 70.14; H, 6.99; N, 3.52; Cl, 9.61.

## Example 13

**3,4-Dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride**

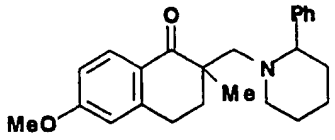



To a solution of the title compound of Example 1 (379 mg, 1.084 mmol, free base) in THF (10 mL) at -78°C under nitrogen with stirring was added a solution of $KN(SiMe_3)_2$ (0.5 M in toluene, 2.39 mL, 1.19 mmol). The reaction mixture was stirred at -78°C for 5 minutes followed by the addition of methyl iodide (0.223 mL, 3.58 mmol). The mixture was stirred at -78°C for another 15 minutes, then kept at -16°C for 0.5 hours followed by the addition of $Et_3N$ (0.832 mL, 5.96 mmol). The mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to afford a thick gummy residue. This was converted to its hydrochloride by treatment with hydrochloric to afford the title compound as a white solid, mp 185-186°C.

**Using methodology analogous to that described for the title compound of Example 13, the compounds of Examples 14 to 20 were prepared:**

**Example 14**

**3,4-Dihydro-6-methoxy-2-methyl-2-[(2-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer A, monohydrochloride**




mp (°C) 178-180.

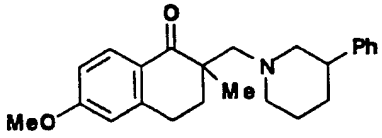
Anal. for: $C_{24}H_{29}NO_2 \bullet HCl \bullet 0.14H_2O$:

Calc'd: C, 71.61; H, 7.58; N, 3.48.

Found: C, 71.78; H, 7.30; N, 3.31.

**Example 15 (isomer A)**

**3,4-Dihydro-6-methoxy-2-methyl-2-[(3-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer A, monohydrochloride**

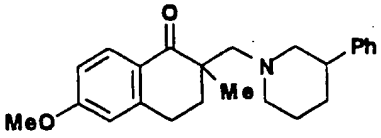



mp (°C) 192-195.

Anal. for: $C_{24}H_{29}NO_2 \bullet HCl$:

**Example 16 (isomer B)**

**3,4-Dihydro-6-methoxy-2-methyl-2-[(3-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer B, monohydrochloride**




mp (°C) 180-182.

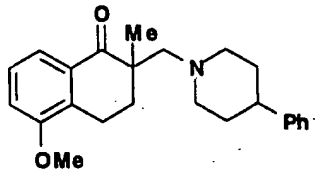
Anal. for: $C_{24}H_{29}NO_2 \cdot HCl \cdot 0.35H_2O$:

Calc'd: C, 70.94; H, 7.62; N, 3.45.

Found: C, 70.96; H, 7.56; N, 3.43.

**Example 17**

**3,4-Dihydro-5-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 190-193.

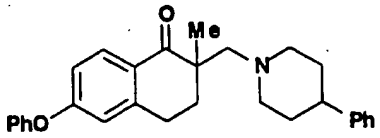
Anal. for: $C_{24}H_{29}NO_2 \cdot HCl \cdot 0.21H_2O$:

Calc'd: C, 71.41; H7.59; N, 3.47.

Found: C, 71.53; H, 7.57; N, 3.35.

**Example 18**

**3,4-Dihydro-2-methyl-6-phenoxy-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 193-194.

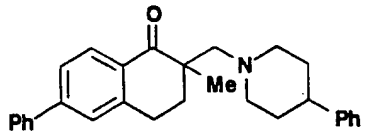
Anal. for: $C_{28}H_{29}NO_2 \cdot HCl \cdot 0.16H_2O$:

Calc'd: C, 74.92; H, 7.01; N, 3.01.

Found: C, 75.01; H, 6.96; N, 2.92.

**Example 19**

**3,4-Dihydro-2-methyl-6-phenyl-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 189-190.

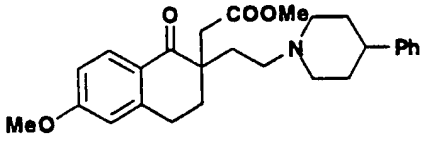
Anal. for: $C_{29}H_{31}NO \cdot HCl \cdot 0.3\ H_2O$:

Calc'd: C, 77.15; H, 7.28; N, 3.10.

Found: C, 77.16; H, 7.16; N, 3.09.

**Example 20**

**1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetic acid, methyl ester, monohydrochloride**




mp (°C) 175-176.

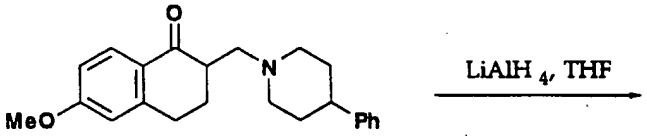
Anal. for: $C_{27}H_{33}NO_4 \cdot HCl \cdot 0.25H_2O$:

Calc'd: C, 68.05; H, 7.30; N, 2.94.

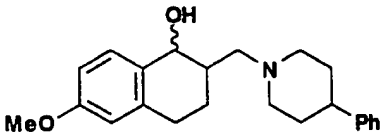
Found: C, 68.04; H, 7.29; N, 2.95.

## Example 21

**trans- and cis-1,2,3,4-Tetrahydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, monohydrochloride**




(Example 1)



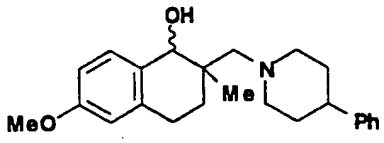

To a solution of the title compound of Example 1 (0.55 g, 1.57 mmol) in THF (10 mL) was added at 0°C under nitrogen with stirring a 1 M solution of lithiumaluminium hydride in THF (2.36 mL, 2.36 mmol). The mixture was allowed to come to room temperature, cooled to 0°C followed by the sequential addition of 1 mL 10% NaOH solution, $MgSO_4$ and ethyl acetate. The mixture was filtered, the filtrate was concentrated and the residue subjected to preparative HPLC (silica gel/hexane-isopropylalcohol-$Et_3N$ 99:1:0.2 to 90:10:0.2 gradient) affording the faster eluting trans isomer as the major product. This was converted to its hydrochloride by treatment with HCl to afford the title compound (trans isomer) as a white solid (385 mg), mp 225-227°C (decomposition).

The slower moving isomer was similarly converted to its hydrochloride to afford the cis compound as a white solid, mp 169-170°C.

**Using methodology analogous to that described for the title compound of Example 21, the compounds of Examples 22 and 23 were prepared:**

**Example 22**

**1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, isomer A**




Isomer A

mp (°C) 160-161.

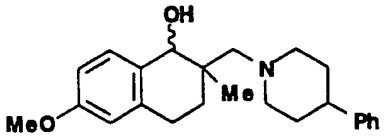
Anal. for: $C_{24}H_{31}NO_2$:

Calc'd: C, 78.87; H, 8.55; N, 3.83.

Found: C, 78.62; H, 8.73; N, 3.74.

**Example 23**

**1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, isomer B, monohydrochloride**




Isomer B

mp (°C) 165-167.

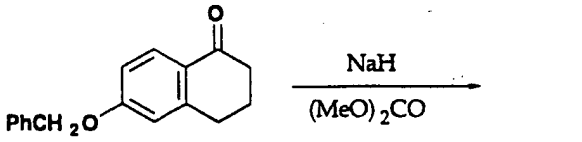
Anal. for: $C_{24}H_{31}NO_2 \cdot HCl \cdot 0.24H_2O$:

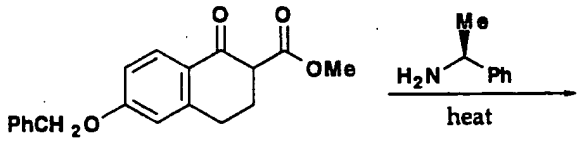
Calc'd: C, 70.95; H, 8.06; N, 3.45.

Found: C, 70.96; H, 8.06; N, 3.36.

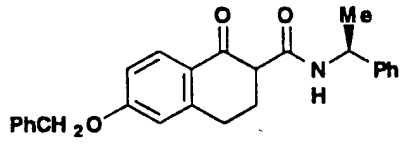
## Example 24

**(1S)-1,2,3,4-Tetrahydro-1-oxo-N-(1-phenylethyl)-6-(phenylmethoxy)-2-naphthalencarboxamide**




1




2

**A. Compound 1:**

A solution of 6-benzyloxy-1-tetralone (12.6 g, 50 mmol) in THF (50 mL) was added over 1 hour to a refluxing mixture of dimethyl carbonate (10.5 mL, 125 mmol) and 60% NaH (ether washed, 7 g, 175 mmol) in THF (75 mL). The recation mixture was refluxed for 14 hours, cooled to room temperature and carefully added to a stirred solution of acetic acid (25 mL) in ether (200 mL). The mixture was washed with water, the organic layer dried over $MgSO_4$ and concentrated to afford an off-white solid (compound 1).

**B. (1S)-1,2,3,4-Tetrahydro-1-oxo-N-(1-phenylethyl)-6-(phenylmethoxy)-2-naphthalencarboxamide**

A mixture of the title A compound (1.44 g, 4.65 mmol) and (S)-α-methylbenzyamine (0.599 mL, 4.65 mmol) in toluene (15 mL) was heated under reflux for 14 hours, concentrated and the crude product was recrystallized from MeOH. The resulting product was heated under reflux for 30 minutes in toluene and concentrated to afford the title compound as an off-white solid.

Anal. for: $C_{26}H_{25}NO_3 \cdot 0.17H_2O$:

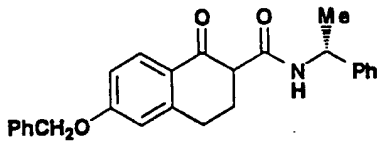
Calc'd: C, 77.58; H, 6.35; N, 3.48.

Found: C, 77.57; H, 5.81; N, 3.40.

**Using methodology analogous to that described for the title compound of Example 24, the compounds of Examples 25 to 29 were prepared:**

**Example 25**

**(1R)-1,2,3,4-Tetrahydro-1-oxo-N-(1-phenylethyl)-6-(phenylmethoxy)-2-naphthalencarboxamide**



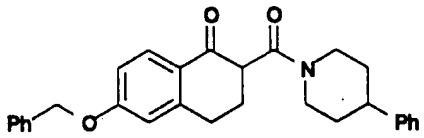

Anal. for: $C_{26}H_{25}NO_3 \cdot 0.22H_2O$:

Calc'd: C, 77.40; H, 6.36; N, 3.47.

Found: C, 77.42; H, 6.16; N, 3.31.

**Example 26**

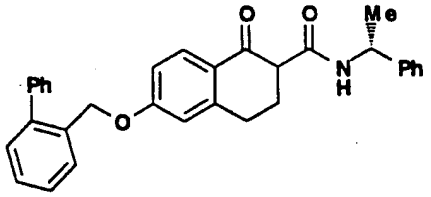
**1-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]carbonyl]-4-phenylpiperidine**



$C_{29}H_{29}NO_3$: m/e = 439.

**Example 27**

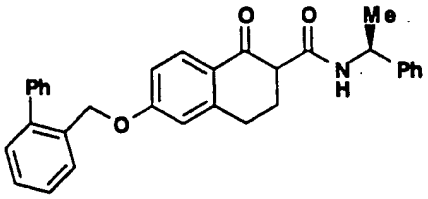
**(1R)-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-N-(1-phenylethyl)-2-naphthalenecarboxamide, 1:1 diastereomer mixture**



$C_{32}H_{29}NO_3$: m/e = 475.

**Example 28**

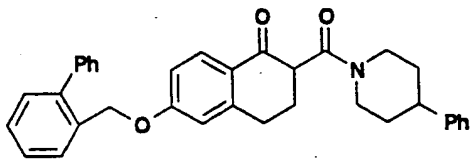
**(1S)-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-N-(1-phenylethyl)-2-naphthalenecarboxamide, 1:1 diastereomer mixture**



$C_{32}H_{29}NO_3$: m/e = 475.

**Example 29**

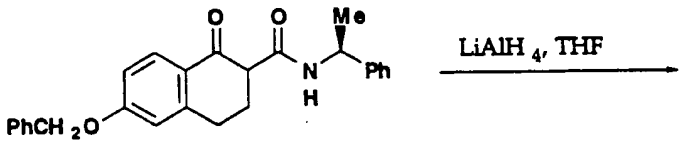
**1-[[6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl]carbonyl]-4-phenylpiperidine**

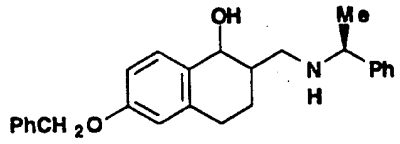


$C_{35}H_{33}NO_3$: m/e = 515.

**Example 30**

**trans-1,2,3,4-Tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-6-(phenylmethoxy)-1-naphthalenol, monohydrochloride**



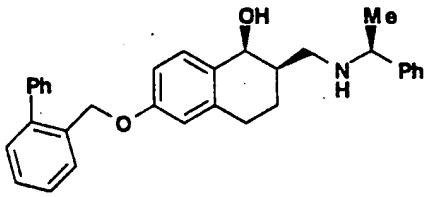
cis and trans

This compound was prepared from the title compound of Example 24 by lithiumaluminium hydride reduction in a manner similar to that described for the synthesis the title compound of Example 21. Purification of the crude product by silica gel chromatography (hexane-isopropyl alcohol-$Et_3N$ 99:1:0.2 to 70:30:0.2) and isolation of the faster moving trans isomers afforded the title compound (white solid) as a 1:1 mixture of the two trans isomers.

**Using methodology analogous to that described for the title compound of Example 30, compounds of Examples 31 to 34 were prepared:**

**Example 31**

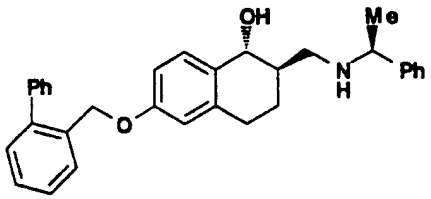
**cis-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-1-naphthalenol**




$C_{32}H_{33}NO_2$: m/e = 463.

**Example 32**

**trans-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-1-naphthalenol, single isomer A**

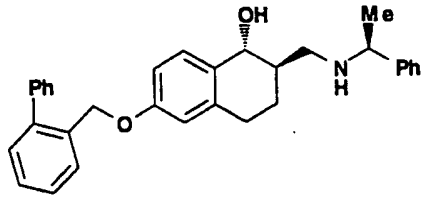



(isomer A)

$C_{32}H_{33}NO_2$: m/e = 463.

**Example 33**

**trans-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]-amino]methyl]-1-naphthalenol, isomer B**

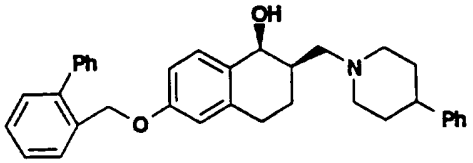



(Isomer B)

$C_{32}H_{33}NO_2$: m/e = 463.

**Example 34**

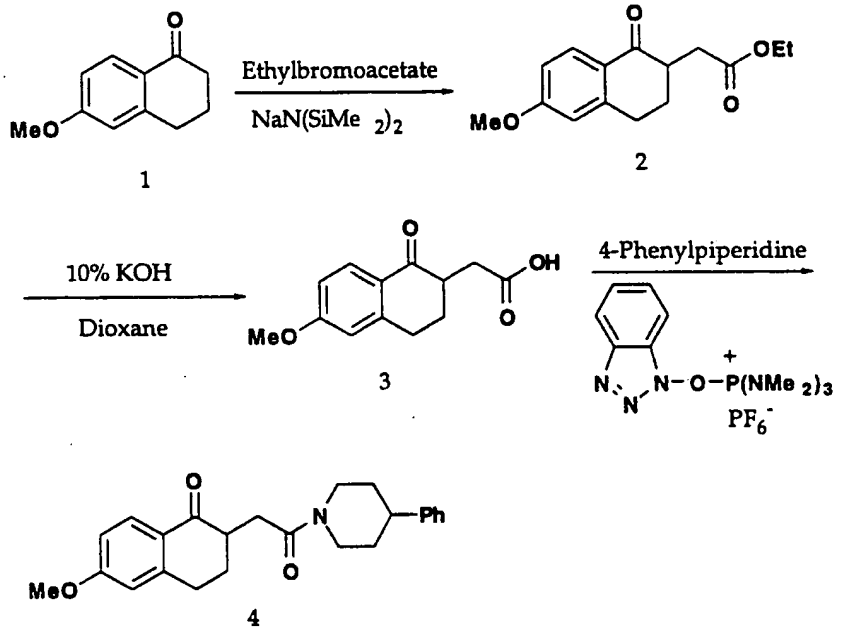
**cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[(4-phenyl-1-piperidinyl)]methyl]-1-naphthalenol**




$C_{35}H_{37}NO_2$: m/e = 475.

## Example 35

**3,4-Dihydro-6-methoxy-2-[2-oxo-2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




### A. Compound 2:

To a solution of 6-methoxy-1-tetralone (1.76 g, 10 mmol) in THF (25 mL) was added at -78°C under nitrogen with stirring a 1M THF solution of sodium hexamethyldisilazide (11 mL, 11 mmol) and the resulting mixture was stirred at 0°C for 5 minutes. The reaction mixture was cooled to -78°C, then added ethyl bromoacetate (1.22 mL, 11 mmol) and stirred at room temperature for 14 hours. The reaction mixture was diluted with ethyl acetate, washed with sodium bicarbonate, dried ($MgSO_4$) and concentrated to afford compound 2 (1.75 g) as a brown gummy solid.

**B. Compound 3:**

To the title A compound (1.75 g) in dioxane (25 mL) was added 10% KOH (25 mL) and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was diluted with water, washed with ether. The aqueous layer was acidified with 10% sulfuric acid and extracted with ethyl acetate. The ethyl actate extract was dried ($MgSO_4$), concentrated and the residue recrystallized from acetone to afford compound 3 (1.45 g) as an orange crystalline solid.

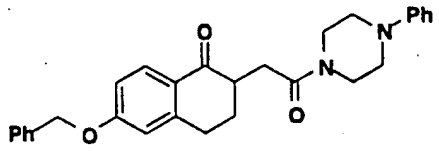
**C. Compound 4:**

To a solution of the title B compound (1.4 g, 5.98 mmol) in dry DMF (10 mL) was added squentially benzotriazole-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate reagent (2.91 g, 6.58 mmol), N-methylmorpholine (0.723 mL, 6.58 mmol) and 4-phenylpiperidine (0.963 g, 5.98 mmol) and the reaction mixture was stirred at room temperature for 14 hours. The mixture was diluted with ethylacetate, washed sequentially with saturated sodium bicarbonate, dilute hydrochloric acid and saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, concentrated, and the residue subjected to flash chromatography (silica gel/hexane-EtOAc 9:1 to 1:1 gradient) to afford compound 4 as a white solid, mp 114-115°C.

**Using methodology analogous to that described for the title compound of Example 35, the compounds of Examples 36 to 54 were prepared:**

**Example 36**

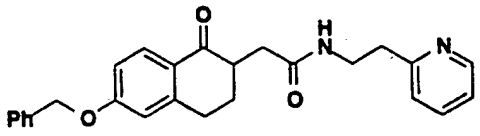
**1-Phenyl-4-[[1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]piperazine**



mp (°C) 169-170.

**Example 37**

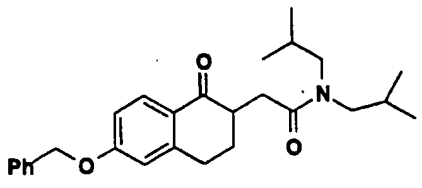
**1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-[2-(2-pyridinyl)ethyl]-2-naphthaleneacetamide**



mp (°C) 112-113.

**Example 38**

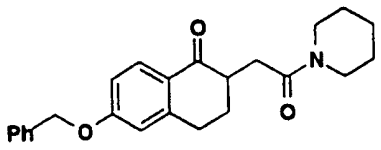
**1,2,3,4-Tetrahydro-N,N-bis(2-methylpropyl)-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide**



mp (°C) 89-90.

**Example 39**

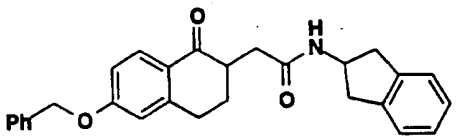
**1-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-piperidine**



mp (°C) 125-126.

**Example 40**

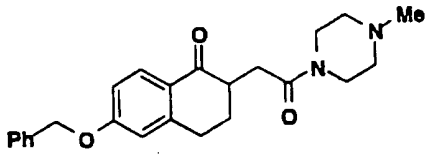
**N-(2,3-Dihydro-1H-inden-2-yl)-1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide**



mp (°C) 162-163.

**Example 41**

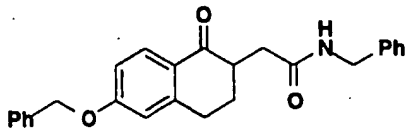
**1-Methyl-4-[[1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]piperazine**



mp (°C) 140-141.

**Example 42**

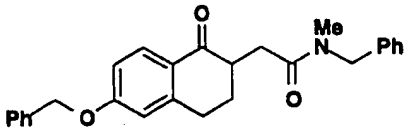
**1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(phenylmethyl)-2-naphthaleneacetamide**



mp (°C) 133-134.

**Example 43**

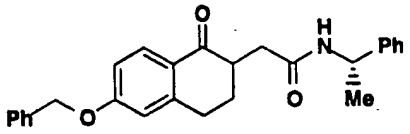
**1,2,3,4-Tetrahydro-1-oxo-N-methyl-6-(phenylmethoxy)-N-(phenylmethyl)-2-naphthaleneacetamide**



mp (°C) 100-101.

**Example 44**

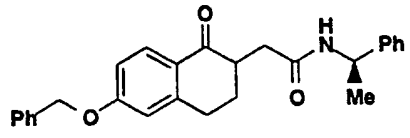
**(1S)-1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(1-phenylethyl)-2-naphthaleneacetamide**



mp (°C) 135-137.

**Example 45**

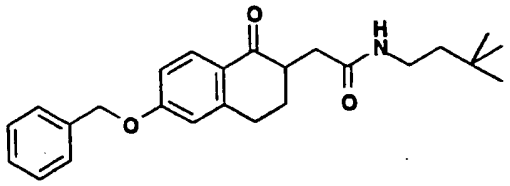
**(1R)-1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(1-phenylethyl)-2-naphthaleneacetamide**



mp (°C) 125-126.

**Example 46**

**N-(3,3-Dimethylbutyl)-1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide**



mp (°C) 93-94.

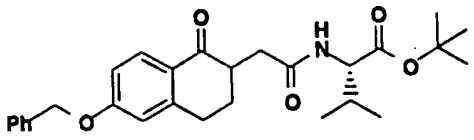
Anal. for: $C_{25}H_{31}NO_3 \cdot 0.144\ H_2$:

Calc'd: C, 77.80; H, 7.96; N, 3.54.

Found: C, 75.80; H, 7.92; N, 3.36.

**Example 47**

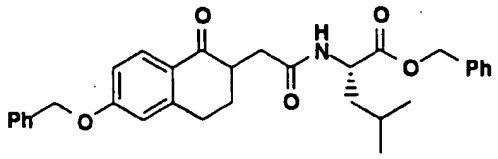
**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, 1,1-dimethylethyl ester**



m/e = 465.

## Example 48

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-leucine, phenylmethyl ester**

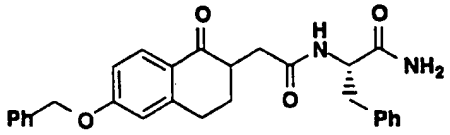


ca. 1:1 mixture of diastereomers

m/e = 513.

## Example 49

**N2-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-phenylalaninamide**

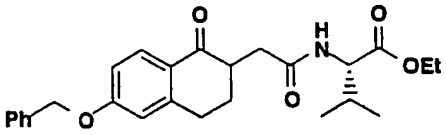


ca. 1:1 mixture of diastereomers

mp (°C) 134-135.

**Example 50**

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, ethyl ester**

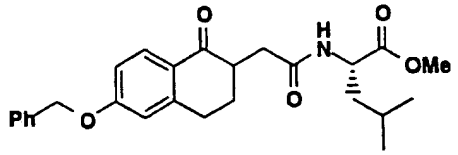


ca. 1:1 mixture of diastereomers

mp (°C) 84-85.

**Example 51**

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-leucine, methyl ester**

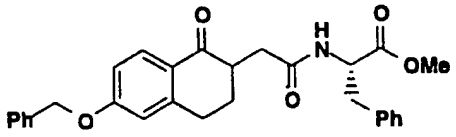


ca. 1:1 mixture of diastereomers

m/e = 437.

**Example 52**

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-phenylalanine, methyl ester**

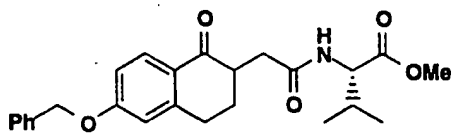


ca. 1:1 mixture of diastereomers

mp (°C) 112-113.

## Example 53

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, methyl ester**

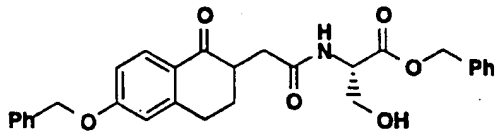



ca. 1:1 mixture of diastereomers

mp (°C) 93-94.

## Example 54

**N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-serine, phenylmethyl ester**

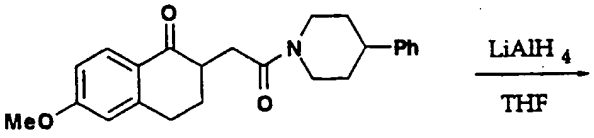



ca. 1:1 mixture of diastereomers

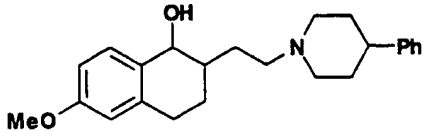
mp (°C) 118-119.

## Example 55

**1,2,3,4-Tetrahydro-6-methoxy-2-(2-(4-phenyl-1-piperidinenyl)-ethyl]-1(2H)-naphthalenol, monohydrochloride**




4




5

To a solution of the title C compound of Example 35 (1.2g, 3.18 mmol) in THF (30 mL) was added at -78°C under nitrogen with stirring a 1M THF solution of lithiumaluminum hydride (9.54 mL, 9.54 mmol). The mixture was stirred at room temperature for 12 hours, quenched by adding 3 mL 10% NaOH and dried over $MgSO_4$. The solids were removed by filtration, the filtrate concentrated and the residue dissolved in ethyl acetate. The solution was filtered through silica gel and the purified product subjected to prep. HPLC (silica/hexane-EtOAc 75:25 to 25:75 gradient) to afford three fractions; fraction 1 (650 mg, pure trans product), fraction 2 (300 mg, ca. 3:1 trans:cis mixture) and fraction 3 (105 mg, 1:1 trans:cis). Fraction 3 was converted to its HCl salt to afford the title compound as a white solid (1:1 mixture of cis:trans alcohols.

mp (°C) 205-207.

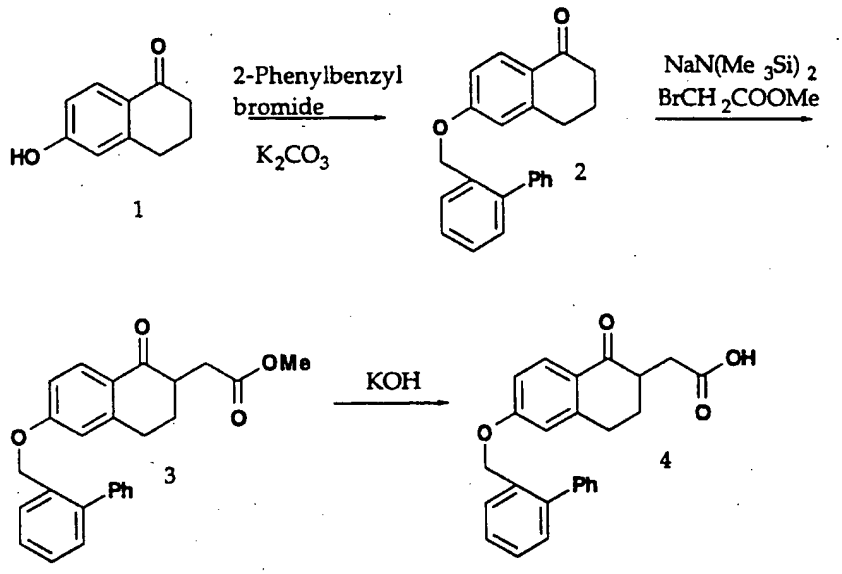
Anal. for: $C_{24}H_{31}NO_2 \cdot HCl \cdot 0.26H_2O$:

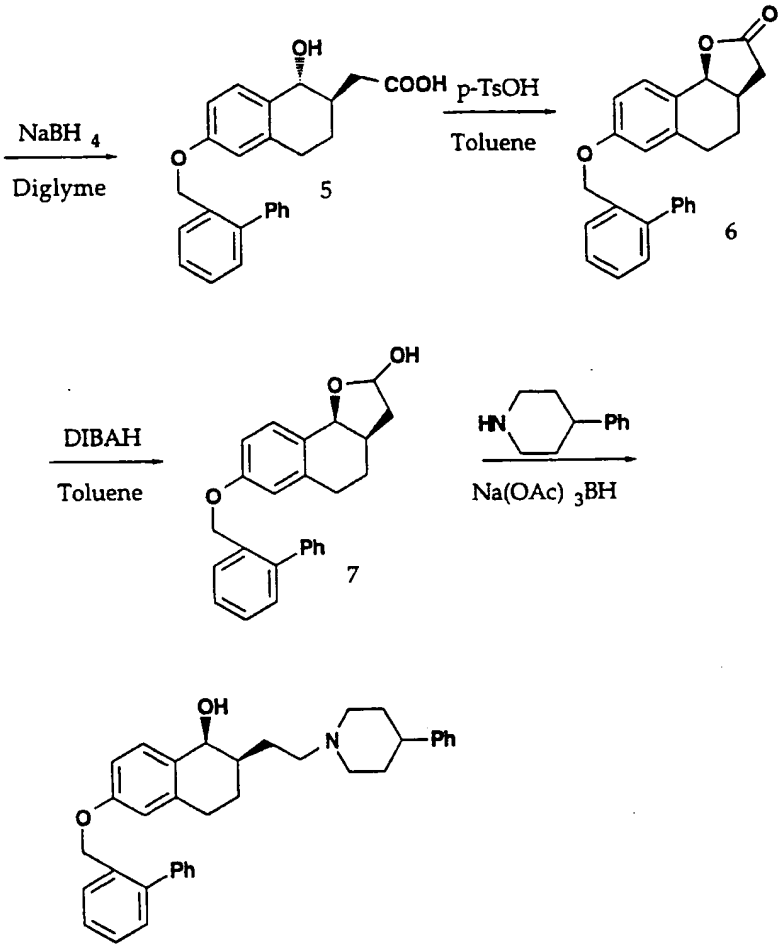
Calc'd: C, 70.88; H, 8.06; N, 3.44.

Found: C, 70.92; H, 7.93; N, 3.40.

## Example 56

**cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)**






**A. Compound 4:**

The title compound was prepared from compound 1 by the same procedure as described for the title B compound of Example 35.

**B. Compound 5:**

To a solution of the keto acid 4 (10 g, 25.8 mmol) in THF (100 mL) was added dropwise to a solution of $NaBH_4$ in diglyme (0.5M, 103.1 mL, 51.6 mmol) at -78°C. The mixture was allowed to come to room temperature and stirred for 30 minutes. The mixture was cooled to 0°C, quenched to pH 4.0 by adding 0.1N HCl, extracted with EtOAc, the

organic layer dried over $MgSO_4$ and concentrated to approximately 75 mL. The resulting clear solution containing compound 5 was diluted with 100 mL toluene, then added p-toluenesulfonic acid momohydrate (100 mg) and refluxed using a Daen-Stark trap for 1.5 hours. The mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, dried over $MgSO_4$, concentrated and the residue recrystallized from EtOAc to afford compound 6 (6.5 g, 68%) as a grey solid.

**C. Compound 7:**

To a solution of the lactone 6 (5 g, 13.6 mmol) in toluene (150 mL) was added at -78°C a solution of DIBAL in toluene (1M, 17.7 mL, 17.7 mmol) with stirring under nitrogen. The mixture was stirred at -78°C for 5 minutes, allowed to come to O°C and stirred for 5 minutes, cooled to -78°C and transferred via a cannula to a stirred (-78°C) mixture of methylene chloride-methanol (95:5). The resulting mixture was allowed to come to room temperature, washed sequentially with 0.1 N HCl and Sat. $NaHCO_3$, the organic layer was dried over $MgSO_4$ and concentrated to afford compound 7 as a gummy white residue (5 g, 55%).

**D. cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)**

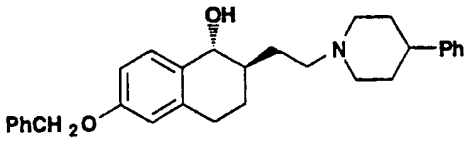
To a solution of compound 7 (0.185 g, 0.5 mmol) and 4-phenylpiperidine (72.5 mg, 0.45 mmol) in 2 mL DMF was added acetic acid (0.029 mL, 0.5 mmol), the mixture was stirred at room temperature for 30 minutes followed by the addition of $Na(OAc)_3BH$ (159 mg, 0.75 mmol). The mixture was stirred at room temperature for 12 hours, diluted with methylene chloride and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was filtered through silica gel using EtOAc to afford the title compound

((208 mg, 80%, free base) as a pale gummy solid. This material was converted to its (1:1) tartaric acid salt to give a white solid, m/e = 516.

**Using methodology analogous to that described for the title compound of Example 56, the compounds of Examples 57 to 73 were prepared:**

**Example 57**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol**




(racemic mixture)

mp (°C) 120-121.

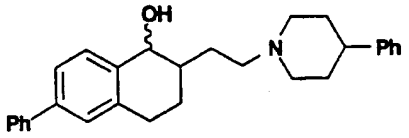
Anal. for: $C_{30}H_{35}NO_2$:

Calc'd: C, 81.59; H, 7.99; N, 3.16.

Found: C, 81.50; H, 8.03; N, 3.09.

**Example 58**

**trans-1,2,3,4-Tetrahydro-6-phenyl-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol**




(trans)

mp (°C) 140-141.

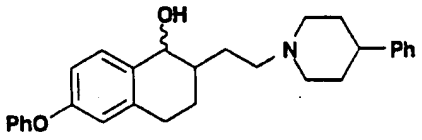
Anal. for: $C_{29}H_{33}NO \cdot 0.08\ H_2O$:

Calc'd: : C, 84.35; H, 8.09; N, 3.39.

Found: C, 84.55; H, 7.79; N, 3.20.

**Example 59**

**trans-1,2,3,4-Tetrahydro-6-phenoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol**




mp (°C) 140-141.

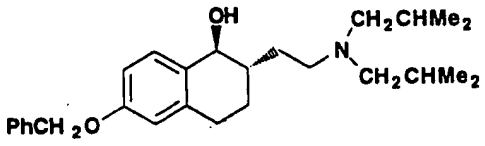
Anal. for: $C_{29}H_{33}NO_2 \cdot 0.09\ H_2O$:

Calc'd: : C, 81.14; H, 7.79; N, 3.26.

Found: C, 81.24; H, 7.67; N, 3.17.

**Example 60**

**trans-2-[2-[Bis(2-methylpropyl)amino]ethyl]-1,2,3,4-tetrahydro--6-(phenylmethoxy)-1-naphthalenol**

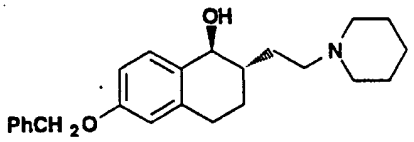



(racemic mixture)

$C_{27}H_{39}NO_2$: m/e = 408.

**Example 61**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(1-piperidinyl)ethyl]-1-naphthalenol**




mp (°C) 88-89.

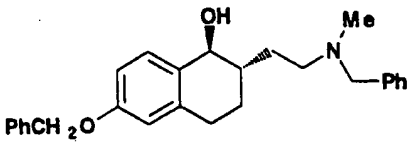
Anal. for: $C_{24}H_{32}NO_2 \cdot 0.27H_2O$:

Calc'd: C, 77.83; H, 8.58; N, 3.78.

Found: : C, 77.82; H, 8.34; N, 3.58.

**Example 62**

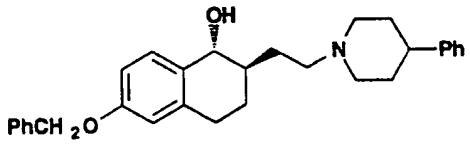
**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[methyl(phenylmethyl)-amino]ethyl]-1-naphthalenol**




$C_{27}H_{31}NO_2$: m/e = 400.

**Example 63**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, enantiomer A**

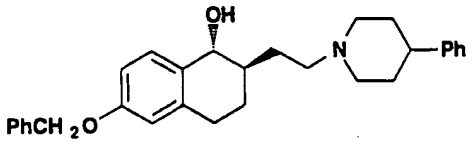



(Enantiomer A)

$C_{30}H_{35}NO_2$:m/e = 440.

**Example 64**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, enantiomer B**

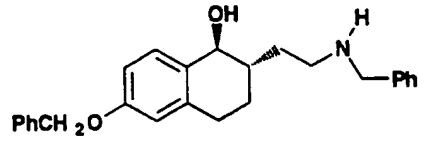



(Enantiomer B)

$C_{30}H_{35}NO_2$:m/e = 440.

**Example 65**

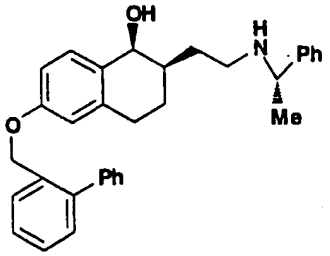
**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer B**




$C_{26}H_{29}NO_2$: m/e = 388.

**Example 66**

**cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)**

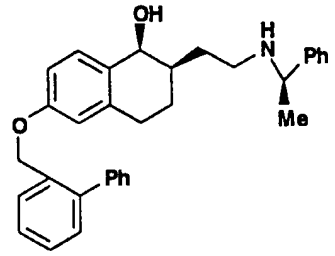



(1:1) mixture of diastereomers

$C_{33}H_{35}NO_2$•tartarate (1:1) salt: m/e = 476.

**Example 67**

**cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(R)-1-phenylethyl]amino]ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)**

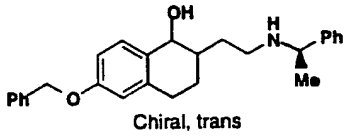



(1:1) mixture of diastereomers

$C_{33}H_{35}NO_2$•tartarate (1:1) salt: m/e = 476.

**Example 68**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(R)-1-phenylethyl]amino]-1-naphthalenol, isomer A, L-tartrate (1:1)**



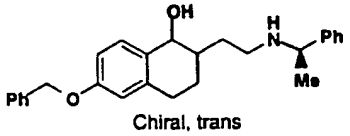

Chiral, trans

(Isomer A)

$C_{33}H_{35}NO_2$•tartarate (1:1) salt: m/e = 476; αD = +44.3° (c = 0.5 $CH_2Cl_2$).

**Example 69**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(R)-1-phenylethyl]amino]-1-naphthalenol, isomer B**



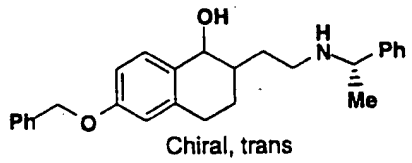

Chiral, trans

(Isomer B)

$C_{33}H_{35}N_2$•tartarate (1:1) salt: m/e = 476; αD = -68° (c = 0.5 $CH_2Cl_2$).

**Example 70**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer A, L-tartrate (1:1)**



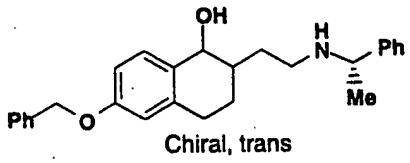

Chiral, trans

(Isomer A)

$C_{33}H_{35}NO_2$•tartarate (1:1) salt: m/e = 476; αD = -44° (c = 0.5 $CH_2Cl_2$).

**Example 71**

**trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer B**




Chiral, trans

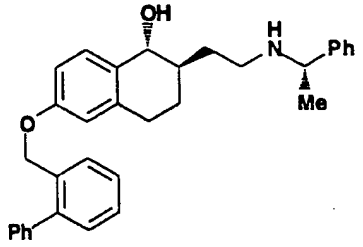
(Isomer B)

mp (°C) 98-99.

$C_{33}H_{35}NO_2$•tartarate (1:1) salt: m/e = 476; αD = -71° (c = 0.5 $CH_2Cl_2$),

**Example 72**

**trans-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, diastereomer A**

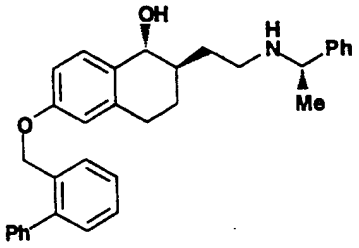



(Isomer A)

$C_{33}H_{35}NO_2$: m/e = 476.

**Example 73**

**trans-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, diastereomer B**

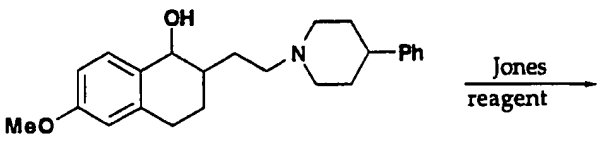



(Isomer B)

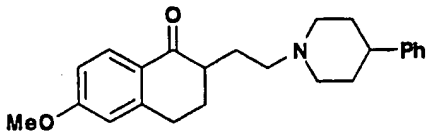
$C_{33}H_{35}NO_2$: m/e = 476.

**Example 74**

**3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]- 1(2H)-naphthalenone, monohydrochloride**




1

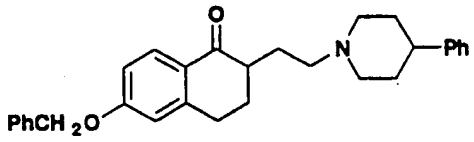



To a solution of the title compound of Example 55 (0.3 g) in 1:1 methylene chloride-acetone (10 mL) was added the Jones reagent (0.5 mL) at 0°C with stirring. The mixture was stirred at room temperature for 5 minutes, diluted with methylene chloride, washed with saturated sodium bicarbonate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by passing through Florisil® eluting with ethyl acetate to give the product as an off-white solid (160 mg). This was treated with hydrochloric and triturated with ether to afford the title compound as a white solid (161 mg, 54%), mp 250-251°C (decomposition).

**Using methodology analogous to that described for the title compound of Example 74, the compounds of Examples 75 to 77 were prepared:**

**Example 75**

**3,4-Dihydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 195-198.

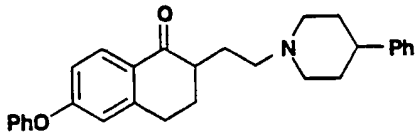
Anal. for: $C_{30}H_{33}NO_2 \bullet HCl \bullet 0.25H_2O$:

Calc'd: C, 74.98; H, 7.24; N, 2.91.

Found: C, 74.97; H, 7.18; N, 2.92.

**Example 76**

**3,4-Dihydro-6-phenoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 223-224.

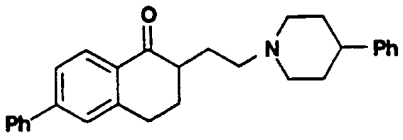
Anal. for: $C_{29}H_{31}NO_2 \bullet HCl \bullet 0.05H_2O$:

Calc'd: C, 75.23; H, 6.99; N3.03.

Found: C, 75.24; H, 7.00; N, 3.02.

**Example 77**

**3,4-Dihydro-6-phenyl-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 237-238.

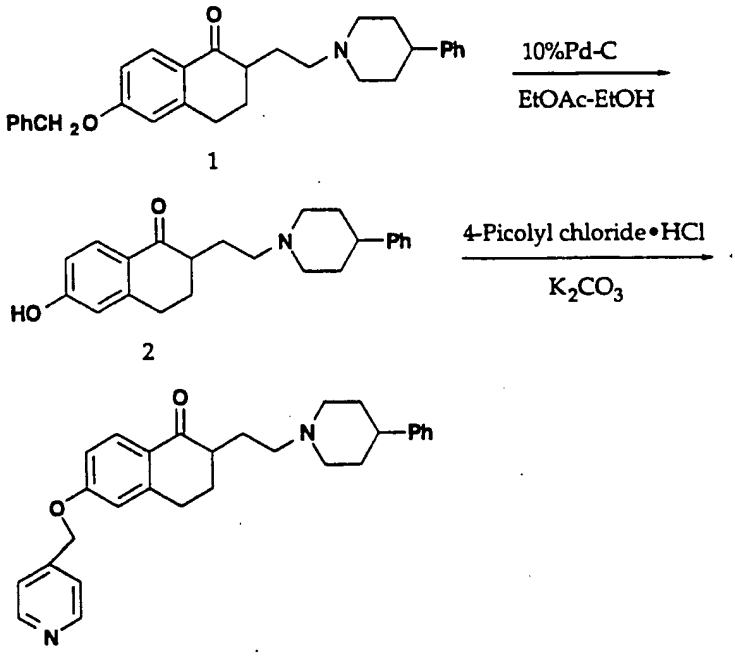
Anal. for: $C_{29}H_{31}NO \bullet HCl \bullet 1.1H_2O$:

Calc'd: C, 74.74; H, 7.40; N, 3.01.

Found: C, 74.75; H, 7.24; N, 3.00.

## Example 78

**3.4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(4-pyridinylmethoxy)010(2H)-naphthalenone, dihydrochloride**




**A. Compound 2:**

A solution of compound 1 (600 mg, 1.36 mmol) in a 4:1 mixture of ethanol/ethyl acetate solution (24 mL) was stirred with 10%Pd-C (120 mg) at room temperature under $H_2$ (balloon) for 2 hours. The reaction mixture was filetered through a Celite pad and evaporated to dryness *in vacuo*. The residue was triturated with hexanes to afford compound 2 as a light tan solid (416 mg, 1.19 mmol, 88% yield), m.p. 175-177°C.

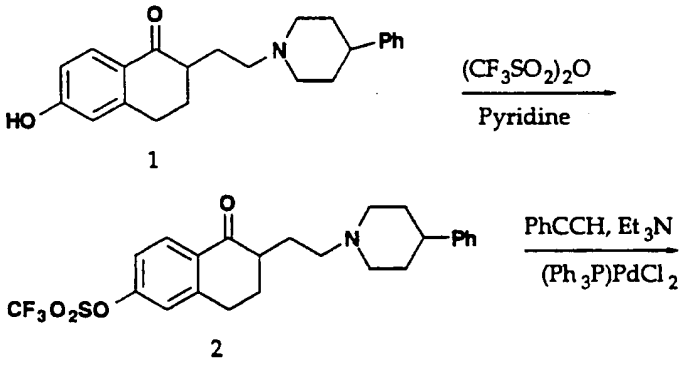
**B. 3.4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(4-pyridinylmethoxy)-1-(2H)-naphthalenone, dihydrochloride**

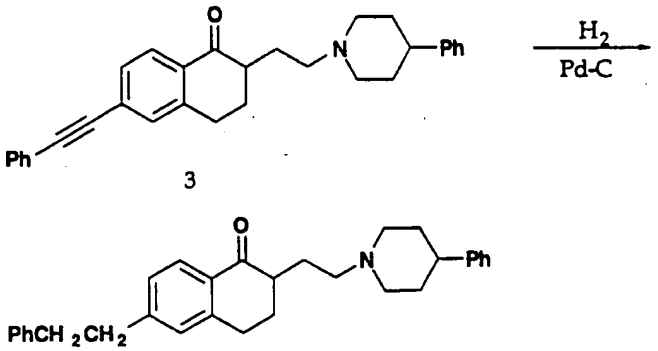
To a stirring solution of compound 2 (86 mg, 0.24 mmol) in dry DMF (3 mL) at 0°C was added pulverized potassium carbonate (170 mg, 1.23 mmol), tetrabutyl-ammonium iodide (9 mg, 0.025 mmol) and 4-

picolylchloride hydrochloride (93 mg, 0.57 mmol). The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate and washed with distilled water. The organic layer was separated and the aqueous layer was backwashed with more ethyl acetate (twice). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a residue which was triturated with diethyl ether to give a brown residue. It was taken up in dichloromethane at 0°C and treated with 4N HCl in dioxane (0.15 mL, 0.61 mmol) to yield a suspension. The suspension was concentrated *in vacuo* and the solid was triturated from ether to afford the title compound (93 mg, 0.18 mmol, 74% yield) as a light brown solid.
mp (°C) 211-213.
Anal. for: $C_{29}H_{34}N_2O_2Cl_2 \cdot 1.73\ H_2O$:
Calc'd: C, 63.94; H, 6.93; N, 5.14.
Found: C, 63.94; H, 6.63; N, 5.05.

**Example 79**

**3,4-Dihydro-6-(2-phenylethyl)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone**






**A. Compound 2:**

A stirring solution of compound 1 (prepared from the title compound of Example 75 by simple hydrogenation) (400 mg, 1.14 mmol) and pyridine (645 mL, 7.98 mmol) in methylene chloride (8 mL) was cooled to 0°C. Trifluoromethanesulfonic anhydride (288 mL, 1.71 mmol) was added and the resulting solution continued to stir under Argon at 0°C for 50 minutes. The reaction mixture was diluted with methylene chloride and sequentially washed with saturated $NaHCO_3$ solution and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to yield a gummy residue (550 mg, 99%).

**B. Compound 3:**

To a solution of compound 2 (220 mg, 0.46 mmol) in dry DMF was added phenylacetylene (93 mg, 0.91 mmol) and triethylamine (274 mL, 1.97 mmol). The resulting solution was stirred under Argon for 1 minute at room temperature. Bis(triphenylphosphine)Pd(II) chloride (32 mg, 0.046 mmol) was added, and the mixture was heated to 90°C for 20 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield as a dark brown residue which was purified by preparative HPLC to give compound 3 (50 mg, 25%) as a yellow solid.

mp (°C) 137-138.

Anal. for: $C_{31}H_{31}NO \cdot 0.33\ H_2O$:

Calc'd: C, 84.70; H, 7.26; N, 3.19.

Found: C, 84.70; H, 7.09; N, 3.10.

**C. 3,4-Dihydro-6-(2-phenylethyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**

Compound 3 (100 mg, 0.23 mmol) was dissolved in a mixture of 4:1 ethanol/ethyl acetate solution (25 mL) and stirred with 10%Pd on carbon (20 mg) at room temperature and under a hydrogen gas (balloon) for 18 hours. The reaction mixture was filtered through a Celite pad and evaporated to dryness. The residue was triturated with hexanes to afford the title compound as a yellow solid (103 mg, 99.9%).

mp (°C) 93-95.

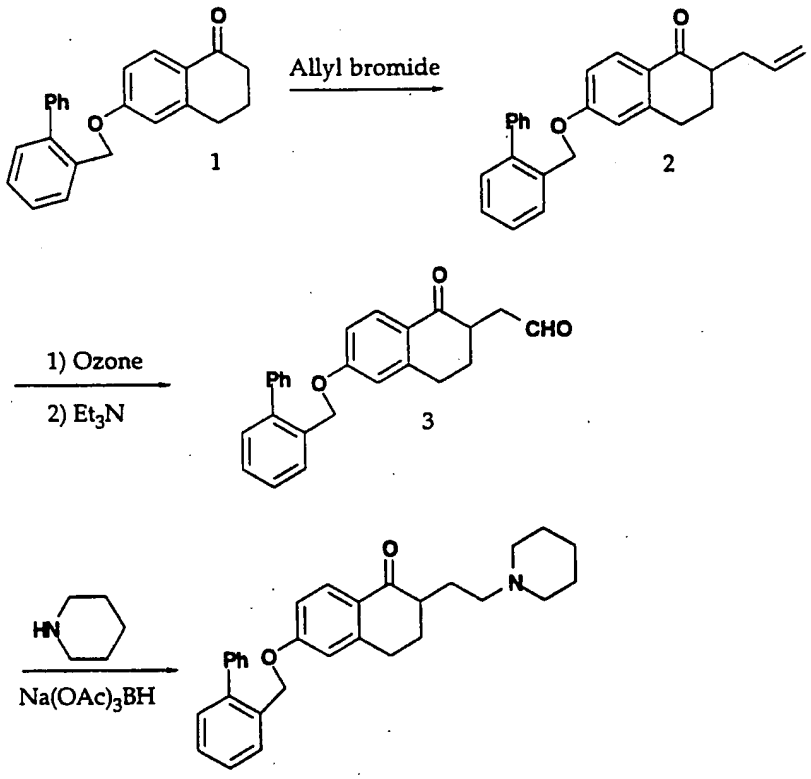
Anal. for: $C_{31}H_{35}NO \cdot 1.052\ H_2O$:

Calc'd: C, 81.55; H, 8.19; N, 3.07.

Found: C, 81.55; H, 8.04; N, 3.14.

## Example 80

**6-[(1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**

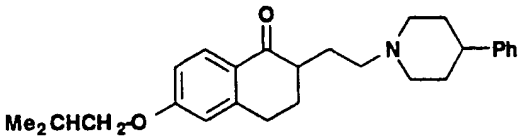



The title compound was prepared from 1 by the same procedure as described for the preparation of title C compound of Example 138a.

**Using methodology analogous to that described for the title compound of Example 80, the compounds of Examples 81 to 123 were prepared:**

**Example 81**

**3,4-Dihydro-6-(2-methylpropoxy)-2-[2-oxo-2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**

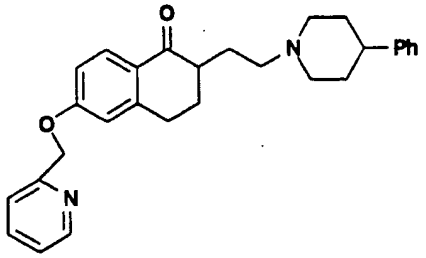



mp (°C) 81-82.

$C_{27}H_{35}NO_2$:

**Example 82**

**3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(4-pyridinylmethoxy)-1(2H)-naphthalenone, dihydrochloride**




mp (°C) 200-201.

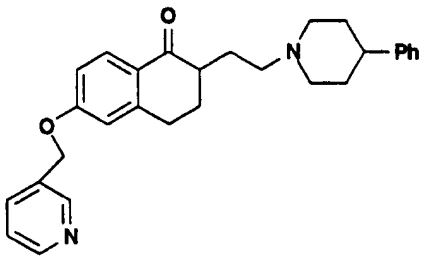
Anal. for: $C_{29}H_{32}N_2O_2 \cdot 2HCl \cdot 1.5\ H_2O$:

Calc'd: C, 64.44; H, 6.90; N, 5.18.

Found: C, 64.10; H, 6.70; N, 5.11.

**Example 83**

**3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(3-pyridinylmethoxy)-1(2H)-naphthalenone, dihydrochloride**




mp (°C) 200-201.

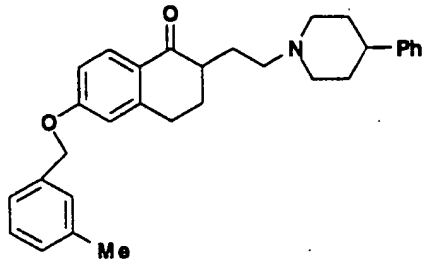
Anal. for: $C_{29}H_{32}N_2O_2 \cdot 2HCl \cdot 2.0\ H_2O$:

Calc'd: C, 63.49; H, 6.96; N, 5.11.

Found: C, 63.19; H, 6.78; N, 5.17.

**Example 84**

**3,4-Dihydro-6-[(3-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**

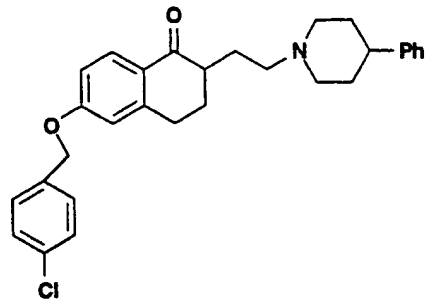



mp (°C) 116-118.

$C_{31}H_{35}NO_2$:

**Example 85**

**6-[(4-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




mp (°C) 139-140.

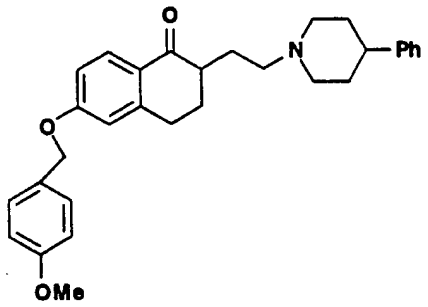
Anal. for: $C_{30}H_{31}NO_2 \cdot HCl \cdot 0.07\ H_2O$:

Calc'd: C, 71.81; H, 6.82; N, 2.95.

Found: C, 75.81; H, 6.58; N, 2.88.

**Example 86**

**3,4-Dihydro-6-[(4-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




mp (°C) 163-164.

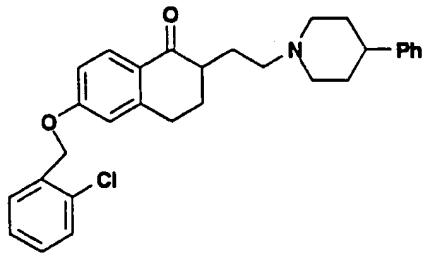
Anal. for: $C_{31}H_{35}NO_3 \cdot 0.33\ H_2O$:

Calc'd: C, 78.29; H, 7.56; N, 2.95.

Found: C, 78.30; H, 7.44; N, 2.77.

**Example 87**

**6-[(2-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



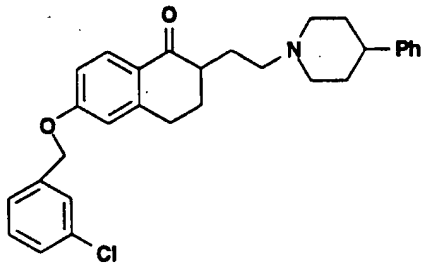

Anal. for: $C_{30}H_{31}NO_2 \bullet HCl$:

Calc'd: C, 76.01; H, 6.80; N, 2.95.

Found: C, 76.06; H, 6.81; N, 2.85.

**Example 88**

**6-[(3-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



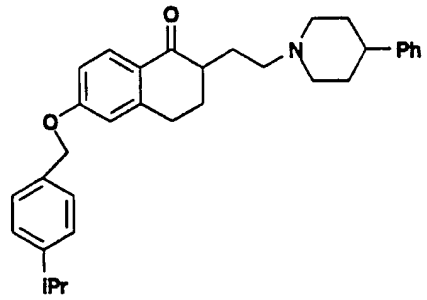

Anal. for: $C_{30}H_{32}NO_2Cl \bullet 0.013\ H_2O$.

Calc'd: C, 75.97; H, 6.81; N, 2.95.

Found: C, 75.97; H, 6.78; N, 2.93.

**Example 89**

**3,4-Dihydro-6-[[4-(1-methyletyl)phenyl]methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




mp (°C) 103-104.

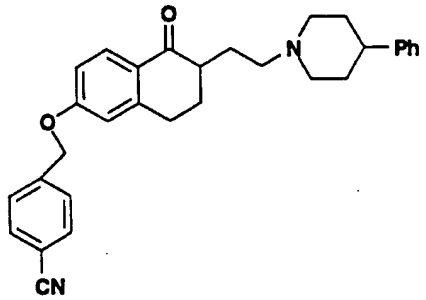
Anal. for: $C_{33}H_{39}NO_2 \cdot 0.16H_2O$:

Calc'd: C, 81.81; H, 8.18; N, 2.89.

Found: C, 81.81; H, 8.11; N, 2.87.

**Example 90**

**4-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile**




mp (°C) 145-146.

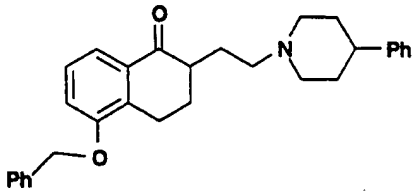
Anal. for: $C_{31}H_{32}N_2O_2 \cdot 0.01\ H_2O$:

Calc'd: C, 80.11; H, 6.94; N, 6.03.

Found: C, 80.11; H, 6.94; N, 5.97.

**Example 91**

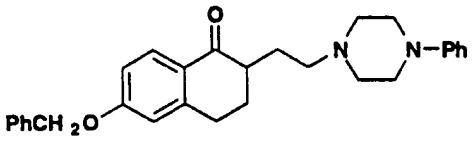
**3,4-Dihydro-5-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, trifluoroacetate (1:1)**



$C_{30}H_{33}NO_2 \bullet CF_3COOH$: m/e = 401.

**Example 92**

**3,4-Dihydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone**



mp (°C) 124-125.

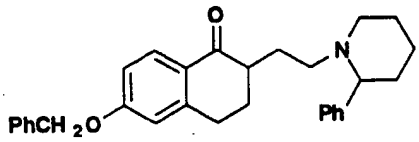
Anal. for: $C_{29}H_{32}N_2O_2$:

Calc'd: C, 79.06; H, 7.32; N, 6.36.

Found: C, 79.01; H, 7.27; N, 6.05.

**Example 93**

**3,4-Dihydro-6-(phenylmethoxy)-2-[2-(2-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, isomer A**



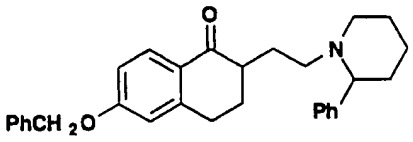
(isomer A)

mp (°C) 105-106.

Anal. for: $C_{30}H_{33}NO_2$:

**Example 94**

**3,4-Dihydro-6-(phenylmethoxy)-2-[2-(2-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, isomer B**



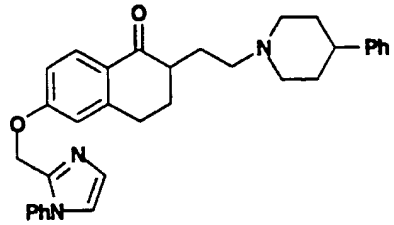

(isomer B)

mp (°C) 94-95.

Anal. for: $C_{30}H_{33}NO_2$:

**Example 94a**

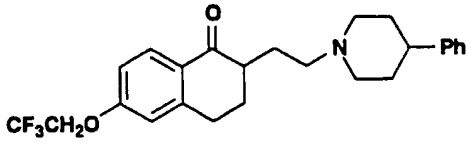
**3,4-Dihydro-6-[(1-phenyl-1H-imidazol-2-yl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




$C_{33}H_{35}N_3O_2$: m/e = 505.

**Example 95**

**3,4-Dihydro-2-[(4-phenyl-1-piperidinyl)ethyl]-6-(2,2,2-trifluoroethoxy)-1(2H)-naphthalenone, monohydrochloride**




mp (°C) 223-225.

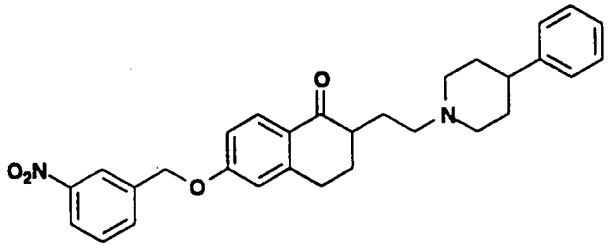
Anal. for: $C_{25}H_{28}NO_2F_3 \cdot HCl$:

Calc'd: C, 64.17; H, 6.25; N, 2.99.

Found: C, 64.43; H, 6.19; N, 2.85.

**Exzample 96**

**3,4-Dihydro-6-[(3-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 114-115.

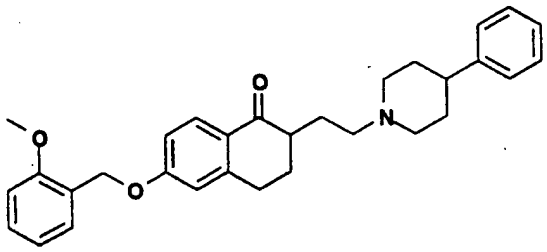
Anal. for: $C_{30}H_{32}N_2O_4 \bullet 0.11\ H_2O$:

Calc'd: C, 74.05; H, 6.67; N, 5.76.

Found: C, 74.05; H, 6.63; N, 5.90.

**Example 97**

**3,4-Dihydro-6-[(2-methoxyphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 119-120.

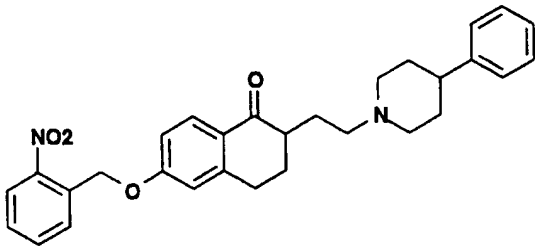
Anal. for: $C_{31}H_{35}NO_3 \bullet 0.02\ H_2O$:

Calc'd: C, 79.22; H, 7.52; N, 2.98.

Found: C, 79.22; H, 7.39; N, 2.77.

**Example 98**

**3,4-Dihydro-6-[(2-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)naphthalenone**




mp (°C) 118-119.

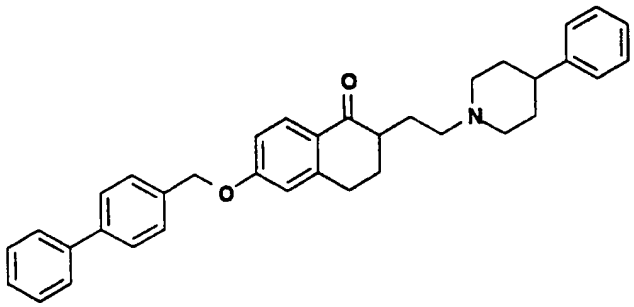
Anal. for: $C_{30}H_{32}N_2O_4 \bullet 0.66\ H_2O$:

Calc'd: C, 73.87; H, 6.69; N, 5.74.

Found: C, 73.87; H, 6.76; N, 5.45.

**Example 99**

**6-([1,1'-Biphenyl]-4-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**




mp (°C) 173-174.

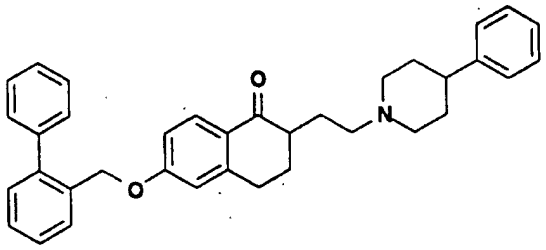
Anal. for: $C_{36}H_{37}NO_2 \bullet 0.22\ H_2O$:

Calc'd: C, 83.21; H, 7.26; N, 2.70.

Found: C, 83.20; H, 7.05; N, 2.74.

**Example 100**

**6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 116-117.

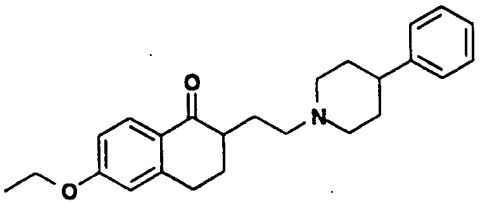
Anal. for: $C_{36}H_{37}NO_2 \bullet 0.30\ H_2O$:

Calc'd: C, 82.98; H, 7.27; N, 2.69.

Found: : C, 82.96; H, 7.12; N, 2.70.

**Example 101**

**3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-ethoxy-1(2H)-naphthalenone**



mp (°C) 85-86.

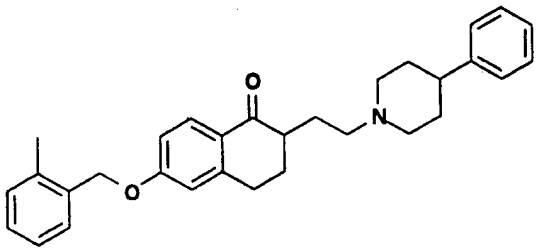
Anal. for: $C_{25}H_{31}NO_2 \bullet 0.00\ H_2O$:

Calc'd: C, 79.54; H, 8.28; N, 3.71.

Found: C, 79.56; H, 8.20; N, 3.60.

**Example 102**

**3,4-Dihydro-6-[(2-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 103-104.

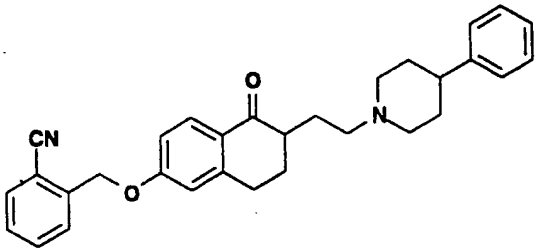
Anal. for: $C_{31}H_{35}NO_2 \cdot 0.027\ H_2O$:

Calc'd: C, 81.99; H, 7.78; N, 3.08.

Found: : C, 81.99; H, 7.69; N, 3.03.

**Example 103**

**2-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile**



mp (°C) 110-111.

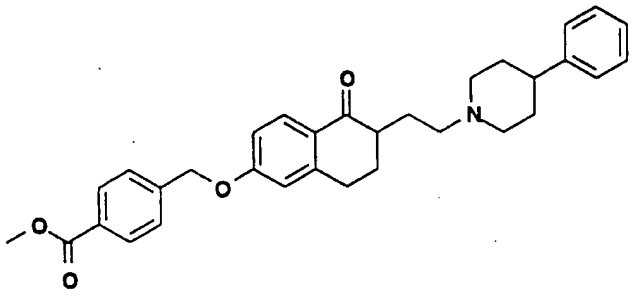
Anal. for: $C_{31}H_{32}N_2O_2 \cdot 0.187\ H_2O$:

Calc'd: C, 79.56; H, 6.97; N, 5.99.

Found: C, 79.56; H, 6.81; N, 5.94.

**Example 104**

**4-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzoic acid, methyl ester**



mp (°C) 160-161.

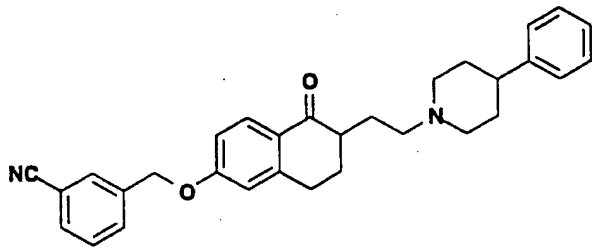
Anal. for: $C_{32}H_{35}NO_4 \cdot 0.01\ H_2O$:

Calc'd: C, 77.21; H, 7.09; N, 2.81.

Found: C, 77.21; H, 7.08; N, 2.78.

**Example 105**

**3-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piper-idinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile**



mp (°C) 124-125.

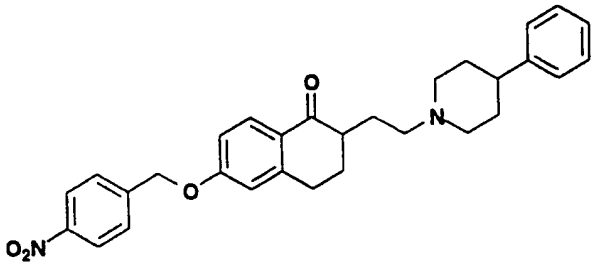
Anal. for: $C_{31}H_{32}N_2O_2 \cdot 0.15\ H_2O$:

Cal'd: C, 79.68; H, 6.97; N, 5.99.

Found: C, 79.68; H, 6.60; N, 5.95.

**Example 106**

**3,4-Dihydro-6-[(4-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 163-164.

MS: $(M+H)^+$ 485.

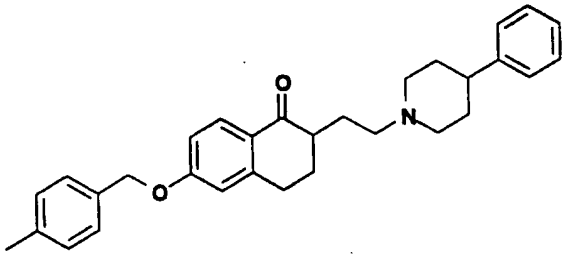
Anal. for: $C_{30}H_{32}N_2O_4 \cdot 0.325\ H_2O$:

Calc'd: C, 73.47; H, 6.71; N, 5.71.

Found: C, 73.47; H, 6.47; N, 5.91.

**Example 107**

**3,4-Dihydro-6-[(4-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 129-131.

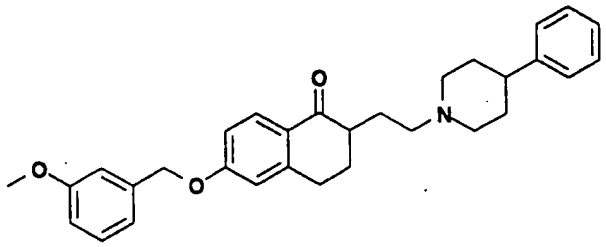
Anal. for: $C_{31}H_{35}NO_2 \cdot 0.697\ H_2O$:

Calc'd: C, 79.87; H, 7.87; N, 3.00.

Found: C, 79.87; H, 7.71; N, 2.90.

**Example 108**

**3,4-Dihydro-6-[(3-methoxyphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



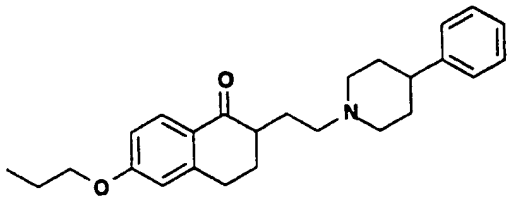
Anal. for: $C_{31}H_{35}NO_3 \cdot 0.225\ H_2O$:

Calc'd: C, 78.61; H, 7.54; N, 2.96.

Found: C, 78.61; H, 7.45; N, 3.22.

**Example 109**

**3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-propoxy-1(2H)-naphthalenone**



mp (°C) 79-80.

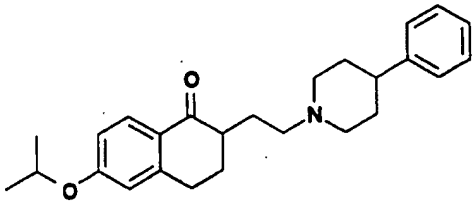
Anal. for: $C_{26}H_{33}NO_2 \cdot 0.077\ H_2O$:

Calc'd: C, 79.47; H, 8.50; N, 3.56.

Found: C, 79.47; H, 8.55; N, 3.50.

**Example 110**

**3,4-Dihydro-6-(1-methylethoxy)-2-[2-(4-phenyl-1-piper-idinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 88-89.

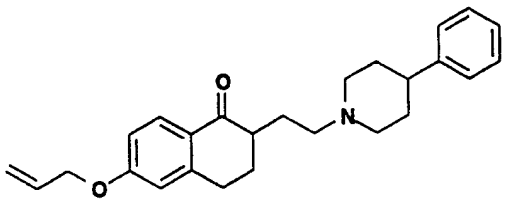
Anal. for: $C_{26}H_{33}NO_2 \cdot 0.235\ H_2O$:

Calc'd: C, 78.90; H, 8.52; N, 3.54.

Found: C, 78.90; H, 8.42; N, 3.42.

**Example 111**

**3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-[(2-propenyl)oxy]-1(2H)-naphthalenone**



mp (°C) 74-75.

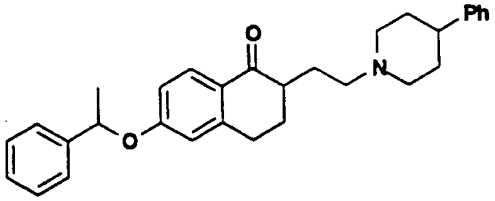
Anal. for: $C_{26}H_{31}NO_2 \cdot 0.197\ H_2O$:

Calc'd: C, 79.44; H, 8.05; N, 3.56.

Found: C, 79.44; H, 7.91; N, 3.44.

**Example 112**

**3,4-Dihydro-6-(1-phenylethoxy)-2-[2-(4-phenyl-1-piper-idinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 158-159.

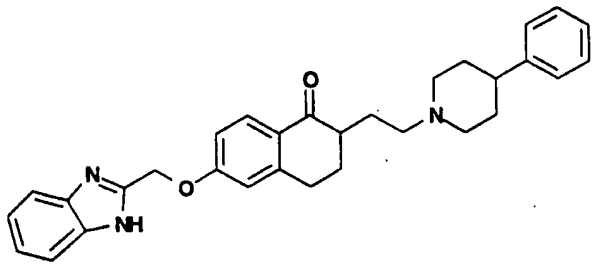
Anal. for: $C_{31}H_{36}NO_2Cl \cdot 0.49\ H_2O$

Calc'd: C, 74.63; H, 7.47; N, 2.81

Found: C, 74.63; H, 7.34; N, 2.84.

**Example 113**

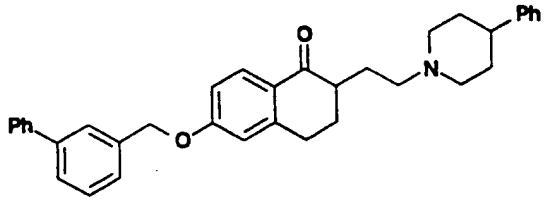
**6-(1H-Benzimidazol-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, dihydrochloride**



mp (°C) 160-162.

**Example 114**

**6-([1,1'-Biphenyl]-3-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 122-123.

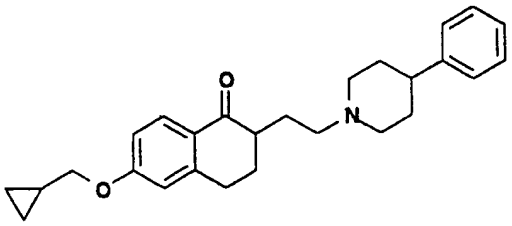
Anal. for: $C_{36}H_{37}NO_2 \bullet 0.185\ H_2O$:

Calc'd: C, 83.31; H, 7.26; N, 2.70.

Found: C, 83.31; H, 7.29; N, 2.59.

**Example 114a**

**6-(Cyclopropylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**



mp (°C) 97-98.

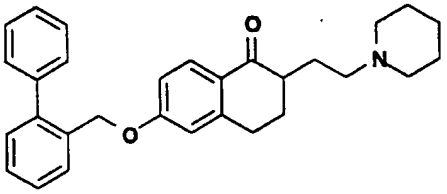
Anal. for: $C_{27}H_{33}NO_2 \cdot 0.161\ H_2O$:

Calc'd: C, 79.78; H, 8.26; N, 3.45.

Found: C, 79.78; H, 8.22; N, 3.38.

**Example 115**

**6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 136-137.

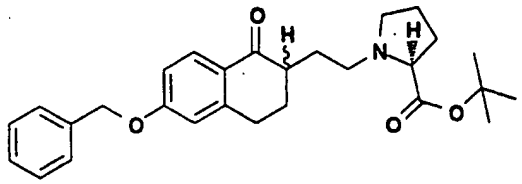
Anal. for: $C_{30}H_{34}NO_2Cl \cdot 1.31\ H_2O$:

Calc'd: C, 72.12; H, 7.39; N, 2.80.

Found: C, 72.11; H, 7.48; N, 2.72.

**Example 116**

**1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-proline, 1,1-dimethylethyl ester**



mp (°C) 62-63.

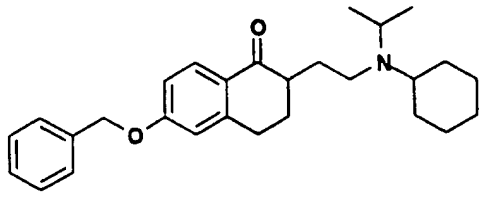
Anal. for: $C_{28}H_{35}NO_4 \cdot 0.08\ H_2O$:

Calc'd: C, 74.56; H, 7.86; N, 3.11.

Found: C, 74.56; H, 7.88; N, 3.10.

**Example 117**

**2-[2-[Cyclohexyl(1-methylethyl)amino]ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone**



mp (°C) 73-74.

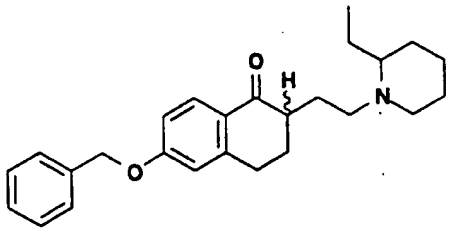
Anal. for: $C_{28}H_{37}NO_2 \cdot 0.10\ H_2O$:

Calc'd: C, 79.81; H, 8.90; N, 3.32.

Found: C, 79.81; H, 8.83; N, 3.12.

**Example 118**

**2-[2-(2-Ethyl-1-piperidinyl)ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone**



mp (°C) 63-64°C.

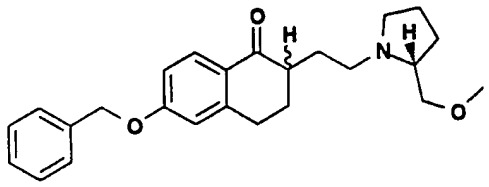
Anal. for: $C_{26}H_{33}NO_2$:

Calc'd: C, 79.76; H, 8.49; N, 3.58.

Found: C, 79.81; H, 8.50; N, 3.53.

**Example 119**

**3,4-Dihydro-2-[2-[(S)-2-(methoxymethyl)-1-pyrrolidinyl]ethyl]-6-(phenylmethoxy)-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 125-127.

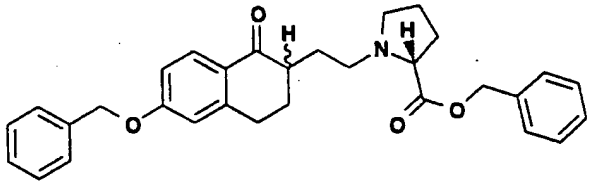
Anal. for: $C_{25}H_{32}NO_3Cl \bullet 0.383\ H_2O$:

Calc'd: C, 68.73; H, 7.56; N, 3.21.

Found: C, 68.73; H, 7.48; N, 2.90.

**Example 120**

**1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-proline, phenylmethyl ester**



mp (°C) 42-43.

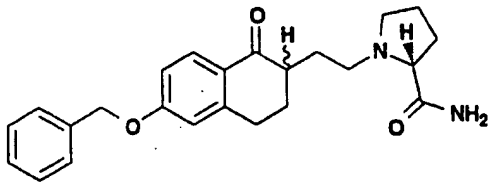
Anal. for: $C_{31}H_{34}NO_4Cl \bullet H_2O$:

Calc'd: C, 68.94; H, 6.76; N, 2.59.

Found: C, 68.94; H, 6.41; N, 2.42.

**Example 121**

**1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-prolinamide**



mp (°C) 168-169.

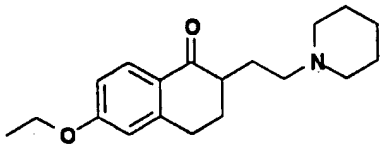
Anal. for: $C_{24}H_{28}N_2O_3 \bullet 2.266H_2O$:

Calc'd: C, 65.52; H, 7.57; N, 6.46.

Found: C, 66,52; H, 6.90; N, 6.22.

**Example 122**

**6-Ethoxy-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride**



mp (°C) 155-156.

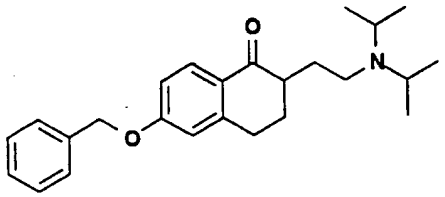
Anal. for: $C_{19}H_{28}NO_2Cl \bullet 0.292\ H_2O$:

Calc'd: C, 66.50; H, 8.40; N, 4.08.

Found: C, 66.50; H, 8.23; N, 3.99.

**Example 123**

**2-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone**



mp (°C) 74-75.

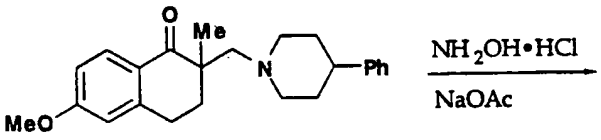
Anal. for: $C_{25}H_{33}NO_2 \cdot 0.04\ H_2O$:

Calc'd: C, 78.96; H, 8.77; N, 3.68.

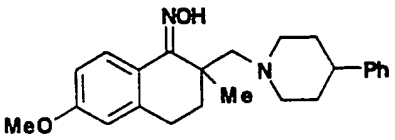
Found: C, 78.96; H, 8.78; N, 3.56.

**Example 124**

**(Z)- and (E)-3,4-Dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime**



1



A mixture of compound 1 (title compound of Example 13) (2.33g, 6.41 mmole), hydroxylamine hydrochloride (2.23g, 32.0 mmole), and sodium acetate (1.89g, 23.1 mmole) in ethanol (46 mL) was heated at 80°C in a sealed pressure bottle. The solvent was removed and the residue was partitioned between 1N sodium hydroxide solution and ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated *in vacuo* to obtain 2.15 g of a tan solid. The crude product was purified by chromatography on silica gel eluting with hexane/ethyl acetate (7/3) containing 0.1% triethylamine

to obtain 0.26g (26%) of (Z)-3,4-dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime.

mp (°C) 169-170.

Anal. for: $C_{24}H_{30}N_2O_2 \bullet 0.33H_2O$:

Calc'd: for C, 74.96; H, 8.04; N, 7.29.

Found: C, 75.07; H, 7.95; N, 7.18.

and 1.0 g (41%) of (E)-3,4-dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone.

mp (°C) 174-176.

Anal. for: $C_{24}H_{30}N_2O_2 \bullet 0.23H_2O$:

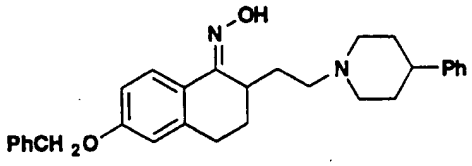
Calc'd: C, 75.32; H, 8.02; N, 7.32.

Found: C, 75.38; H, 7.96; N, 7.26.

**Using methodology analogous to that described for the title compound of Example 124, the compounds of Examples 125 to 133 were prepared:**

**Example 125**

**3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime, monohydrochloride**




mp (°C) 205-208.

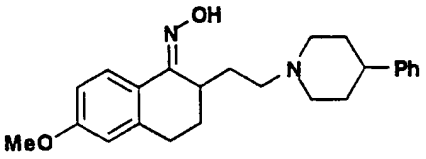
Anal. for: $C_{30}H_{34}N_2O_2 \bullet HCl \bullet 0.42H_2O$:

Calc'd: C, 72.27; H, 7.24; N, 5.62.

Found: C, 72.29, H, 7.24; N, 5.60.

**Example 126**

**3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime**




mp (°C) 167-168.

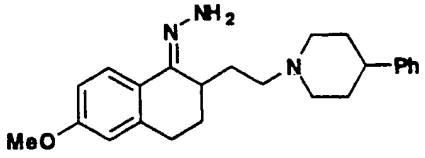
Anal. for: $C_{24}H_{30}N_2O_2 \cdot 0.79H_2O$:

Calc'd: C, 73.39; H, 8.10; N, 7.13.

Found: C, 73.47, H, 7.84; N, 7.05.

**Example 127**

**3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone hydrazone**




mp (°C) 161-162.

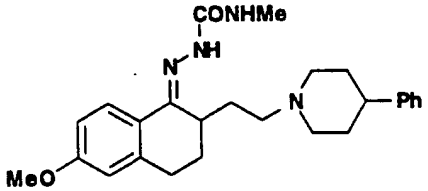
Anal. for: $C_{24}H_{31}N_3O \cdot 0.28H_2O$:

Calc'd: C, 75.36; H, 8.31; N, 11.04.

Found: C, 75.31; H, 8.21; N, 11.04.

**Example 128**

**N-Methyl-2-[3,4-dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenylidene]-hydrazinecarboxamide**




mp (°C) 84-85.

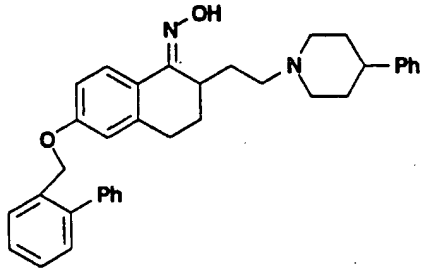
Anal. for: $C_{26}H_{34}N_4O_2 \cdot 0.68\ H_2O$:

Calc'd: C, 69.88; H, 7.98; N, 12.54.

Found: C, 69.81; H, 7.88; N, 11.90.

**Example 129**

**(E)-6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime**




mp (°C) 78-79.

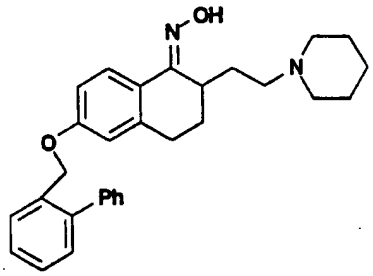
Anal. for: $C_{36}H_{38}N_2O_2 \cdot 0.27\ H_2O$:

Calc'd: C, 80.74; H, 7.25; N, 5.23.

Found: C, 80.74; H, 7.37; N, 4.84.

**Example 130**

**(E)-6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime**




mp (°C) 70-71.

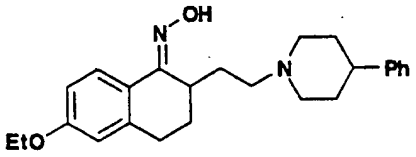
Anal. for: $C_{30}H_{34}N_2O_2 \cdot 1.3\ H_2O$:

Calc'd: C, 75.41; H, 7.72; N, 5.86.

Found: C, 75.41; H, 7.26; N, 5.71.

**Example 131**

**(E)-6-Ethoxy-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime**



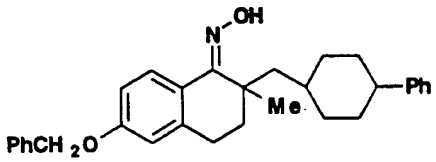

Anal. for: $C_{25}H_{32}N_2O_2 \cdot 0.21\ H_2O$:

Calc'd: C, 75.75; H, 8.25; N, 7.07.

Found: C, 75.75; H, 8.14; N, 6.74.

**Example 132**

**(E)-3,4-Dihydro-2-methyl-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime**




mp (°C) 158-159.

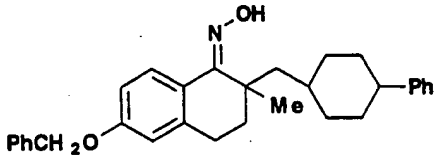
Anal. for: $C_{30}H_{34}N_2O_2 \cdot 0.02\ H_2O$:

Calc'd: C, 79.20; H, 7.54; N, 6.16.

Found: C, 79.20; H, 7.57; N, 5.96.

**Example 133**

**(Z)-3,4-Dihydro-2-methyl-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime**




mp (°C) 116-117.

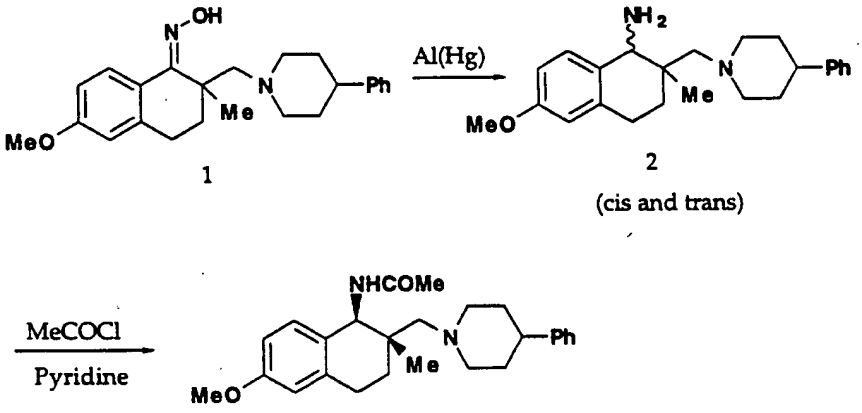
Anal. for: $C_{30}H_{34}N_2O_2 \cdot 0.02\ H_2O$:

Calc'd: C, 79.20; H, 7.54; N, 6.16.

Found: C, 79.19; H, 7.54; N, 5.98.

**Example 134**

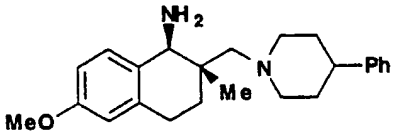
**trans-N-[1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenyl]acetamide**




**A. 1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenamine**

A suspension containing compound 1 (1.5 g, 3.96 mmol, title compound of Example 124) and excess Al(Hg) in tetrahydrofuran/water (40 mL, 90:10) was heated under reflux for 18 hours. The reaction mixture was cooled to room temperature, filtered and the filtrate was washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (10% methanol in dichloromethane) to give

two products which were converted to their hydrochloride salts by treatment with hydrochloric acid.



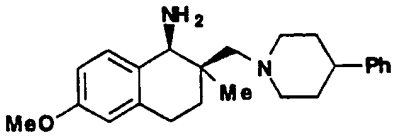

trans-isomer (543 mg, 37.6%).

mp (°C) 195-205 (decomposition).

Anal. for: $C_{24}H_{32}N_2O \cdot 2HCl \cdot 0.9H_2O$:

Calc'd: C, 63.49; H, 7.96; N, 6.17; Cl, 15.62.

Found: C, 63.50; H, 7.94; N, 6.11; Cl. 15.29.




cis-isomer (543 mg, 37.6%).

mp (°C) 217-219 (decomposition).

Anal. for: $C_{24}H_{32}N_2O \cdot HCl \cdot 0.9H_2O$:

Calc'd: C,71.89; H, 8.29; N, 6.99

Found: C, 71.76; H,8.35; N, 6.99.

**B. trans-N-[1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenyl]-acetamide**

To a solution of compound 2 (trans isomer) 205 mg, 0.56 mmole) and pyridine (0.2 mL) in methylene chloride (2.0 mL) cooled to 0°C was added acetyl chloride (48.6 mg). The reaction mixture was stirred at room temperature for two hours and partitioned between 1N sodium hydroxide solution and ethyl acetate. The organic fraction was washed with saturated sodium chloride solution and dried over sodium sulfate.

The solvent was recovered *in vacuo* to obtain 203 mg of a white solid. The crude product was purified by crystallization from hexane/ethyl acetate to obtain the title compound (180 mg, 79) as a white solid.

mp (°C) 186-188.

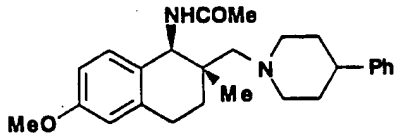
Anal. for: $C_{26}H_{34}N_2O_2$:

Calc'd: C, 76.81; H, 8.43; N, 6.89.

Found: C, 76.68; H, 8.44; N, 6.88.

**Example 135**

**cis-N-[1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenyl]acetamide**




The title A compound of Example 134 (cis isomer, 153 mg, 0.42 mmol) was converted to the desired product in the same manner as described for the title compound of Example 133, part B. The product was purified by crystallization from isopropyl ether to obtain the title compound as a colorless solid (141 mg, 83%).

mp (°C) 140-142.

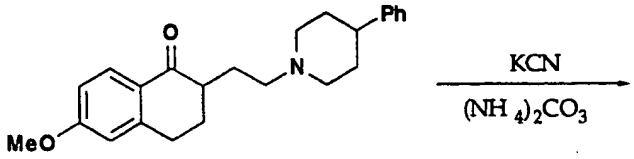
Anal. for: $C_{26}H_{34}N_2O_2$:

Calc'd: C, 76.81; H, 8.43; N, 6.89.

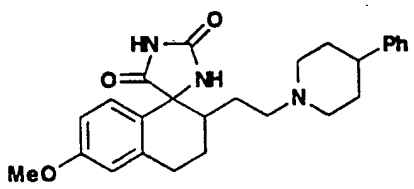
Found: C, 76.71; H, 8.52; N, 6.79.

**Example 136**

**1',2',3',4'-Tetrahydro-6'-methoxy-2'-[2-(4-phenyl-1-piperidinyl)ethyl]spiro[imidazolidine-4,1'(2'H)-naphthalene]-2,5-dione**




1

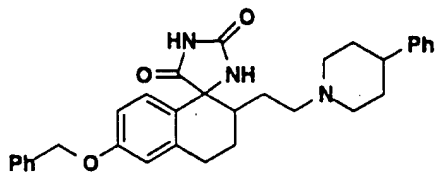



A mixture of compound 1 (free base, 0.95 g, 2.62 mmol, title compound of Example 74), potassium cyanide (0.596 g, 9.16 mmol) and ammonium carbonate (3.27 g, 34 mmol) in formamide (40 mL) was heated in a 50 mL sealed tube at 75°C for 12 hours and then at 115-120°C for 50 hours. The mixture was poured over cold aqueous solution of $NaHCO_3$, stirred for 10 minutes, filtered, and the solid product recrystallized repeatedly from hot DMF to give the title compound as a white solid (isomer A), mp 242-243°C. The mother liquor was concentrated and the residue recrystallized from for DMF to afford the title compound as a white solid, m. p. 288-289.

**Using methodology analogous to that described for the title compound of Example 136, the compound of Example 137 were prepared:**

**Example137**

**1',2',3',4'-Tetrahydro-6'-(phenylmethoxy)-2'-[2-(4-phenyl-1-piperidinyl)ethyl]spiro[imidazolidine-4,1'(2'H)-naphthalene]-2,5-dione, isomer A**

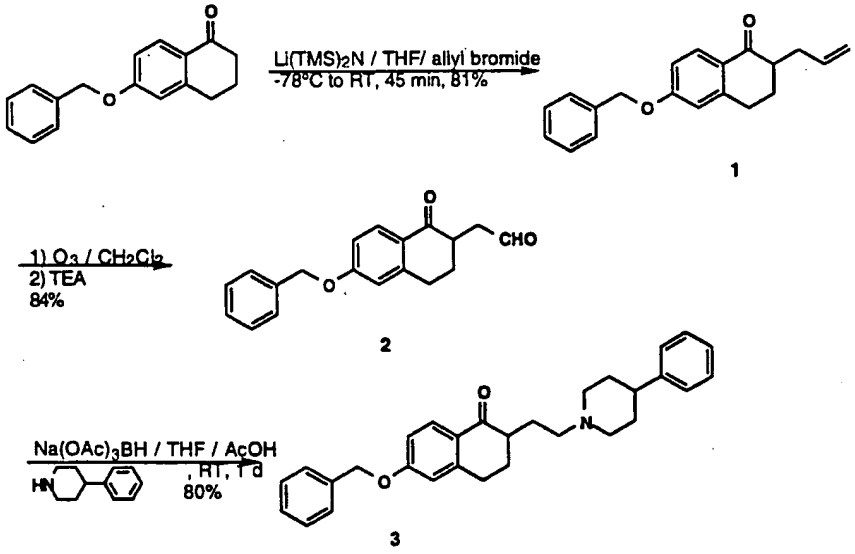


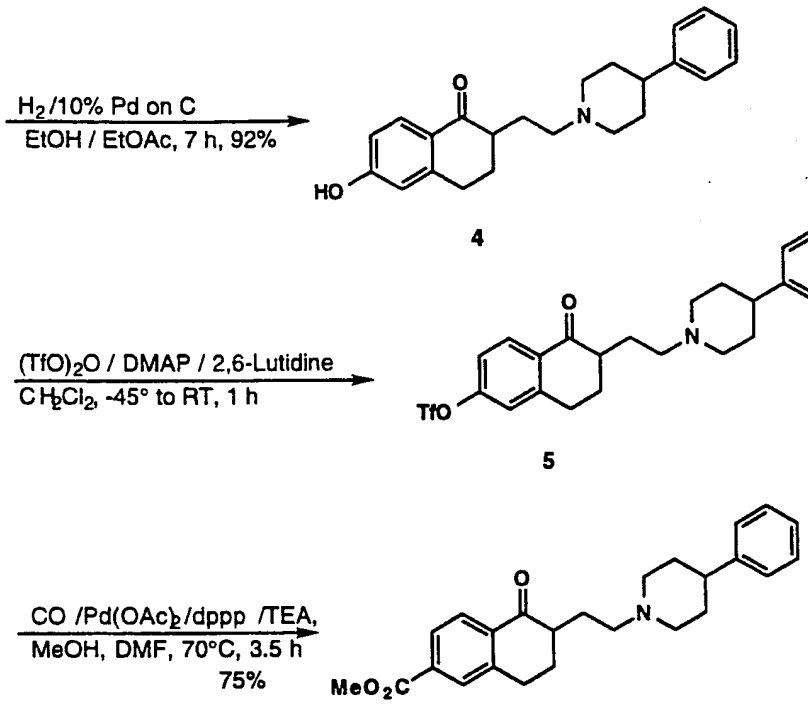
Isomer A: mp 245-246°C.

Isomer B: mp 275-246°C.

## Example 138

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, methyl ester**






**A. 3,4-Dihydro-2-(2-propenyl)-6-(phenylmethoxy)-1(2H)naphthalenone**

Lithium bis(trimethylsilyl)amide (1 M in THF, 150 mL, 0.15 mol) was added over 20 minutes to a solution of 6-benzyloxytetralone (37 g, 0.14 mol) in dry THF (580 mL) stirring at -78°C under argon in a flame dried flask. HMPA (26 mL, 0.15 mol) was added and then the -78°C bath was replaced with a 0°C bath. After 10 minutes, allyl bromide (49 mL, 0.58 mol) was added quickly in one portion. After stirring at ambient temperature for 45 minutes, the reaction was quenched with water (56 mL). The reaction was transferred to a separatory funnel with ether/1 N HCl. Extraction with ether (2 x 600 mL), washing the combined organic layers with water, saturated $NaHCO_3$, water, and brine, and drying over $MgSO_4$ afforded 48 g of crude product. A series of 4 flash

chromatographies (silica, 75 mm dia., 10% EtOAc/hexane) afforded 34 g (81%) of the title compound. $R_f$ (silica, 25% EtOAc/hexane) = 0.50.

**B. 1,2,3,4-Tetrahydro-6-(phenylmethoxy)-1-oxo-2-naphthaleneacetaldehyde**

Ozone generated by a Welsbach Ozonizer was bubbled into a solution of the title A compound (16 g, 55 mmol) in $CH_2Cl_2$ (1 l) stirring at -78°C until the blue color persisted (~2 hours). Nitrogen was then bubbled through the reaction to discharge the blue color and then for 30 minutes after the blue color had dissapated. Triethylamine (16 mL, 110 mmol) was added dropwise over 15 minutes and the reaction was stirred at ambient temperature. After 1 hour, the reaction was transferred to a separatory funnel and washed with 0.5 M HCl, water, and brine and dried over $MgSO_4$ to afford 18 g of crude product after evaporation of the solvent. Flash chromatography (silica, 75 mm dia., 25% EtOAc/hexane and flushed with EtOAc) afforded 14 g (84%) of the title compound. $R_f$ (silica, 25% EtOAc/hexane) = 0.20.

**C. 3,4-Dihydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)naphthalenone**

Sodium triacetoxyborohydride (14 g, 64 mmol) was added to a stirring solution of 4-phenylpiperidine (7.4 g, 46 mmol), the title B compound (12 g, 41 mmol), and acetic acid (2.4 mL, 41 mmol) in THF (360 mL). After stirring at ambient temperature for 1 day, the reaction was diluted with $CH_2Cl_2$ and transferred to a separatory funnel. Washing the combined organic layers with 1/2 saturated $NaHCO_3$ and brine and drying over $MgSO_4$ afforded 19 g of crude product after evaporation of the solvent. Recrystallization from ethanol afforded 12 g of product. Flash chromatography (silica, 50 mm dia., 3%

MeOH/$CH_2Cl_2$) of the mother liquors afforded an additional 3.9 g (total 16 g, 80%) of the title compound.

**D. 3,4-Dihydro-6-hydroxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)naphthalenone**

A suspension of 10% Pd/C (3.3 g) and the title C compound (16 g, 37 mmol) in ethanol (630 mL) and ethyl acetate (160 mL) was stirred under a balloon of hydrogen. After 7 hours, the reaction was filtered through a pad of Celite (AFA) rinsing with $CH_2Cl_2$. The filtrate was evaporated *in vacuo* to afford 12 g (92%) of the title compound.

**E. 3,4-Dihydro-6-(trifluoromethanesulfonyloxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)naphthalenone**

4-Dimethylaminopyridine (0.83 g, 6.8 mmol) was added to a solution in phenol of the title D compound (12 g, 34 mmol) in $CH_2Cl_2$ (dried by passing through a column of Act. I alumina, 280 mL) stirring at -45°C. 2,6-Lutidine (4.8 mL, 41 mmol) and triflic anhydride (6.8 mL, 41 mmol) were then added and the cold bath was removed. After stirring at ambient temperature for 1 hour, the reaction was transferred to a separatory funnel with ether (500 mL). Washing the organic layer with water (250 mL), 0.5 M HCl (250 mL), saturated $NaHCO_3$ (250 mL), and brine (250 mL) and drying over $Na_2SO_4$ afforded the title compound (15 g) as a pink solid after evaporation of the solvent.

**F. 5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, methyl ester**

Palladium acetate (31 mg, 0.14 mmol) and 1,3-bis(diphenylphosphino)propane (57 mg, 0.14 mmol) were added to a solution of the title E compound (2.2 g, 4.6 mmol) and triethylamine (1.3 mL, 9.2 mmol) in methanol (1.5 mL) and dimethylformamide (8 mL). Carbon monoxide was bubbled through the resulting mixture for

10 minutes and then the reaction was stirred under a balloon of CO at 70°C. After 3.5 hours, the reaction was diluted with $CH_2Cl_2$ (100 mL) and washed with brine (2 x 40 mL) to afford 1.8 g of crude product after evaporation of the solvent. Flash chromatography (silica, 37 mm dia., 3% MeOH/$CH_2Cl_2$) afforded 1.4 g (75%) of the title compound. mp 110.0-112.0°C; LRMS (Electrospray, 0.1% $NH_4OH$/$CH_3CN$, pos. ion spectrum) m/z 392 (M+1); $R_f$ (silica, 5% MeOH/$CH_2Cl_2$) = 0.15.

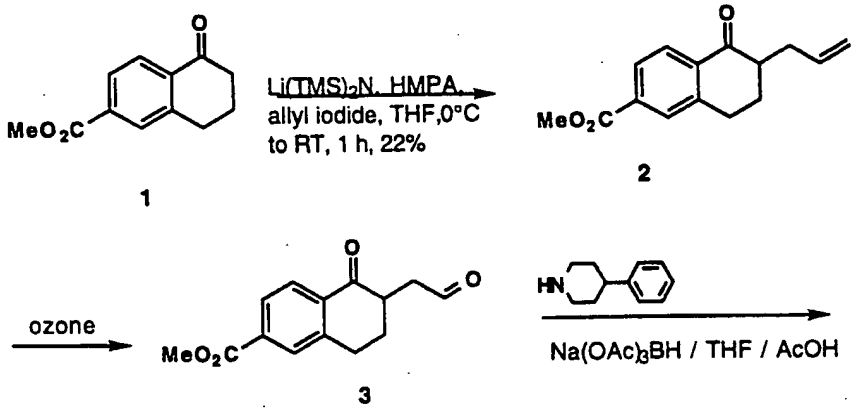
Anal. for: $C_{25}H_{29}NO_3 \cdot 0.66\ H_2O$:

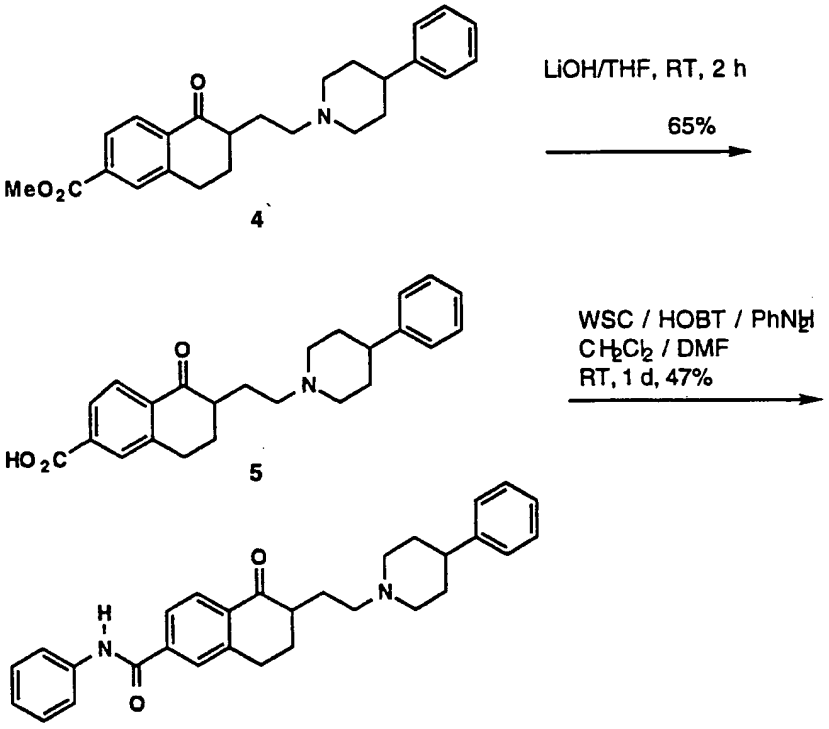
Calc'd: C, 74.42; H, 7.58; N, 3.47.

Found: C, 74.42; H, 7.41; N, 3.17.

**Example 138a**

**5,6,7,8-Tetrahydro-5-oxo-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**






**A. Compound 2:**

Lithium bis(trimethylsilyl)amide (1 M in THF, 5.1 mL, 5.1 mmol) was added over 12 minutes to a solution of 1 (1.1 g, 5.4 mmol) in dry THF (22 mL) stirring at -78°C under argon in a flame dried flask. HMPA (1.0 mL, 5.5 mmol) was added and then the -78°C bath was replaced with a 0°C bath. After 10 minutes, allyl iodide (2.0 mL, 22 mmol) was added quickly in one portion. After stirring at ambient temperature for 65 minutes, the reaction was quenched with water (22 mL). The reaction was transferred to a separatory funnel with ether/1 N HCl. Extraction with ether (2 x 150 mL), washing the combined organic layers with water, saturated $NaHCO_3$, water, and brine, and drying over $MgSO_4$ afforded 1.6 g of crude product. Flash chromatography (silica, 50 mm dia., 40% to 80% $CH_2Cl_2$/hexane) afforded 0.73 g (66%) of 5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-2-naphthalenecarboxylic acid, methyl ester. $R_f$ (silica, 30% $CH_2Cl_2$/hexane) = 0.12.

**B. 5,6,7,8-Tetrahydro-5-oxo-6-(formylmethyl)-2-naphthalenecarboxylic acid, methyl ester**

Ozone generated by a Welsbach Ozonizer was bubbled into a solution of **2** (0.90 g, 4.0 mmol) in $CH_2Cl_2$ (60 mL) stirring at -78°C until the blue color persisted (~10 minutes). Nitrogen was then bubbled through the reaction to discharge the blue color and then for 30 minutes after the blue color had dissipated. Hunig's base (1.4 mL, 8.0 mmol) was added dropwise over 5 minutes and the reaction was stirred at ambient temperature. After 1 hour, the reaction was transferred to a separatory funnel and washed with 0.5 M HCl (30 mL), $H_2O$ (2 x 20 mL), and brine and dried over $MgSO_4$ to afford 1.0 g of crude product after evaporation of the solvent. Flash chromatography (silica, 37 mm dia, 50% EtOAc/hexane) afforded 0.60 g (66%) of the desired aldehyde.

**C. 5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)-ethyl]-2-naphthalenecarboxylic acid, methyl ester**

Sodium triacetoxyborohydride (0.86 g, 4.0 mmol) was added to a stirring solution of 4-phenylpiperidine (0.62 g, 3.9 mol), aldehyde **2** (0.60 g, 2.6 mmol), and acetic acid (0.15 mL, 2.6 mmol) in THF (23 mL). After stirring at ambient temperature for 1 day, the reaction was diluted with and transferred to a separatory funnel. Washing with 1/2 saturated $NaHCO_3$ and brine and drying over $MgSO_4$ afforded 1.4 g of crude product after evaporation of the solvent. Flash chromatography (silica, 37 mm dia, 5% MeOH/ $CH_2Cl_2$) afforded 0.77 g (75%) of the title compound.

**D. 5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)-ethyl]-2-naphthalenecarboxylic acid**

Lithium hydroxide (1 M in $H_2O$, 1.2 mL, 1.2 mmol) was added to a solution of the title C compound (0.48 g, 1.2 mmol) in THF (12 mL). After

stirring at ambient temperature for 2 hours, the reaction was evaporated *in vacuo* to afford 0.47 g of crude product. Chromatography (HP-20 rinsed with 200 mL $H_2O$, 25 mm dia., $H_2O$, 5% step gradient of 50 mL each from 0% to 50% acetone/$H_2O$) afforded 0.31 g (65%) of the title compound. mp 118.0-120.0°C.

Anal. for: $C_{24}H_{27}NO_3 \cdot 0.71\ H_2O$:

Calc'd: C, 73.85; H, 7.34; N, 3.59.

Found: C, 73.85; H, 7.50; N, 3.72.

**E. 5,6,7,8-Tetrahydro-5-oxo-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**

1-hydroxybenzotriazole hydrate (HOBT, 80 mg, 0.58 mmol) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (WSC, 0.17 g, 0.56 mmol) were added to a solution of title D compound (0.20 g, 0.53 mmol) in $CH_2Cl_2$ (2.5 mL) and DMF (0.64 mL) stirring at ambient temperature. After stirring for 30 minutes, aniline (65 mg, 0.70 mmol) in $CH_2Cl_2$ (0.3 mL) was added. After stirring at ambient temperature for 24 hours, water (20 mL) was added and the pH brought to 4.5 with 1 N HCl. Extraction with $CH_2Cl_2$ (2 x 20 mL), washing the combined organic layers with sat. $NaHCO_3$ and brine, and drying over $MgSO_4$ afforded 0.20 g of crude product after evaporation of the solvent. Flash chromatography (silica, 15 mm dia, 5% MeOH/$CH_2Cl_2$) afforded 0.14 g of product. Recrystallization from $CH_2Cl_2$/hexane afforded 0.11 g (47%) of the title compound. mp (°C) 182.0-184.5.

Anal. for: $C_{30}H_{32}N_2O_2 \cdot 0.65\ H_2O$:

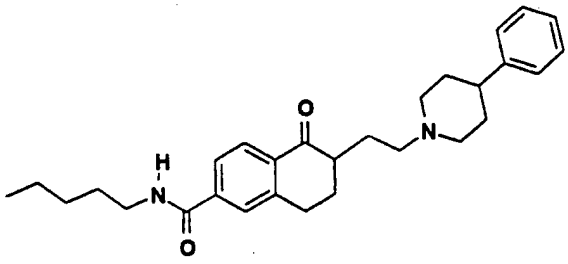
Calc'd: C, 77.61; H, 7.23; N, 6.03.

Found: C, 77.61; H, 7.04; N, 6.25.

**Using methodology analogous to that described for the title compound of Example 138, the compounds of Examples 139 to 144 were prepared:**

**Example 139**

**5,6,7,8-Tetrahydro-5-oxo-N-pentyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 128.0-131.0.

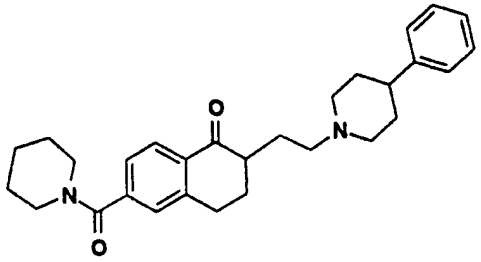
Anal. for: $C_{29}H_{38}N_2O_2$:

Calc'd: C, 77.99; H, 8.58; N, 6.27.

Found: C, 78.16; H, 8.35; N, 6.44.

**Example 140**

**1-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]piperidine**



mp (°C) 109.0-110.0.

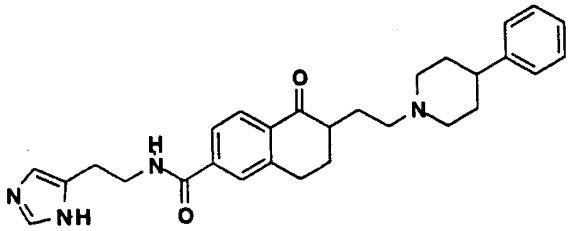
Anal. for: $C_{29}H_{36}N_2O_2 \cdot 0.38\ H_2O$:

Calc'd: C, 77.14; H, 8.21; N, 6.20.

Found: C, 77.12; H, 8.16; N, 6.47.

**Example 141**

**5,6,7,8-Tetrahydro-N-(1H-imidazol-2-yl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, dihydrochloride**



mp (°C) 200.0-204.0.

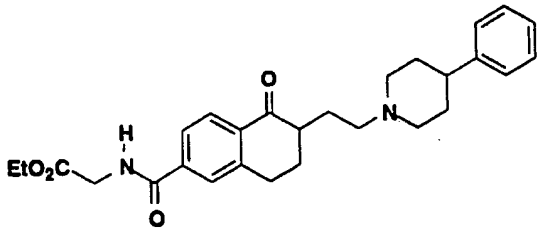
Anal. for: $C_{29}H_{34}N_4O_2 \cdot 2\ HCl \cdot 2.10\ H_2O$:

Calc'd: C, 59.90; H, 6.97; N, 9.63.

Found: C, 59.93; H, 7.04; N, 9.46.

**Example 142**

**2-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]acetic acid, ethyl ester**



mp (°C) 140.0-142.5.

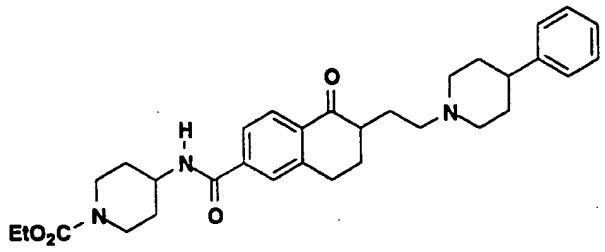
Anal. for: $C_{28}H_{34}N_2O_4 \cdot 0.25\ H_2O$:

Calc'd: C, 72.01; H, 7.44; N, 6.00.

Found: C, 72.01; H, 7.31; N, 5.88.

**Example 143**

**4-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]-1-piperidinecarboxylic acid, ethyl ester**



mp (°C) 204.0-206.5.

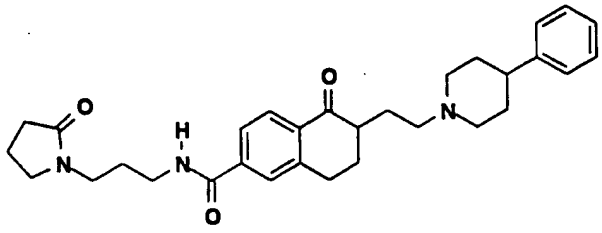
Anal. for: $C_{32}H_{41}N_3O_4 \cdot 0.28\ H_2O$:

Calc'd: C, 71.62; H, 7.71; N, 7.75.

Found: C, 71.62; H, 7.80; N, 7.83.

**Example 144**

**5,6,7,8-Tetrahydro-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



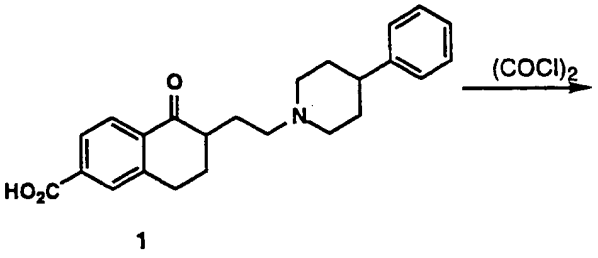
Anal. for: $C_{31}H_{39}N_3O_3 \cdot 0.15\ CH_2Cl_2 \cdot 1.12\ H_2O$:

Calc'd: C, 69.99; H, 7.94; N, 7.64.

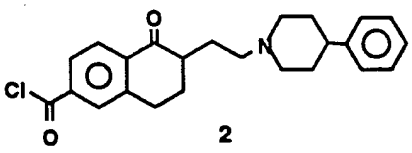
Found: C, 69.99; H, 7.83; N, 7.86.

**Example 145**

**N-([1,1-Biphenyl]2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**

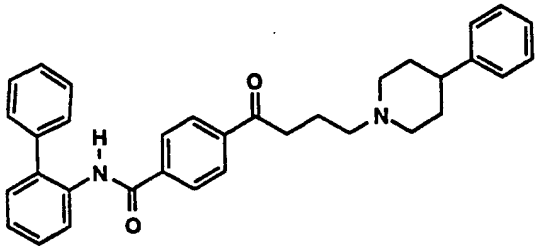



1




2

Hunig's base / $CH_2Cl_2$ / 2-$NH_2$-biphenyl
RT, 2 h, 44%




**A. Compound 2:**

Oxalyl chloride (2 M in $CH_2Cl_2$, 0.10 mL, 0.20 mmol) was added to a solution of 1, the title compound of Example 138a, part D (60 mg, 0.16 mmol) in $CH_2Cl_2$ (1.0 mL) stirring in a flame dried flask under argon containing a catalytic amount of DMF. After stirring at ambient temperature for 30 minutes, the reaction was evaporated *in vacuo* to give 2.

**B. (BMS 201761)**

Compound 2 was dissolved in $CH_2Cl_2$ (1 mL) and diisopropylethyl amine (62 mg, 0.09 mL, 0.48 mmol) was added followed by 2-amino biphenyl (20 mg, 0.21 mmol). After stirring at ambient temperature for 2 hours, the reaction was transferred to a separatory funnel with

water/$CH_2Cl_2$. Extraction with $CH_2Cl_2$ (2 x 20 mL) and drying over $MgSO_4$ afforded 0.24 g of crude product after evaporation of the solvent. Flash chromatography over silica gel (3% MeOH/$CH_2Cl_2$) afforded 37 mg (44%) of product. This material was combined with another batch and converted to its hydrochloride salt by addition of HCl (4 N in dioxane, 1 eq) to yield the title compound. mp 218.0-222.5°C.

Anal. for: $C_{36}H_{36}N_2O_2 \cdot HCl \cdot 0.32\ H_2O$:

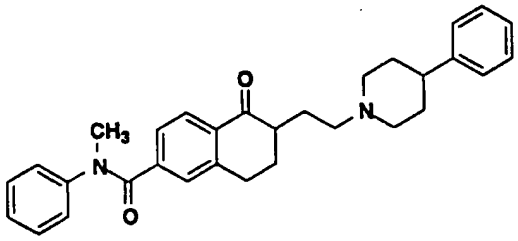
Calc'd: C, 75.74; H, 6.65; N, 4.91.

Found: C, 75.74; H, 6.62; N, 4.82.

**Using methodology analogous to that described for the title compound of Example 145, the compounds of Examples 146 to 189 were prepared:**

**Example 146**

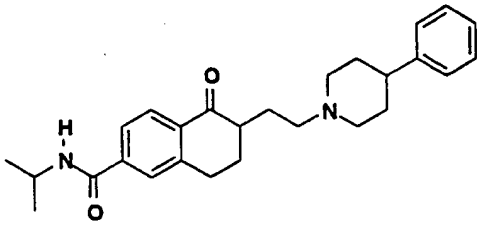
**5,6,7,8-Tetrahydro-5-oxo-N-methyl-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**




mp (°C) 123.0-126.0.

**Example 147**

**5,6,7,8-Tetrahydro-N-(1-methylethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 164.0-165.5.

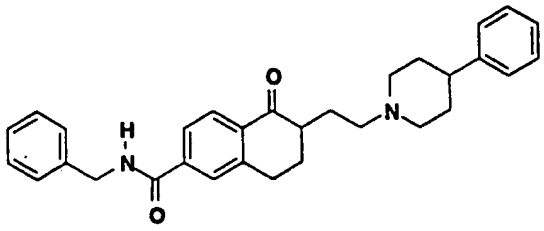
Anal. for: $C_{27}H_{34}N_2O_2 \cdot 0.79\ H_2O$:

Calc'd: C, 74.93; H, 8.29; N, 6.47.

Found: C, 74.94; H, 8.06; N, 6.28.

**Example 148**

**5,6,7,8-Tetrahydro-5-oxo-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 130.0-133.0.

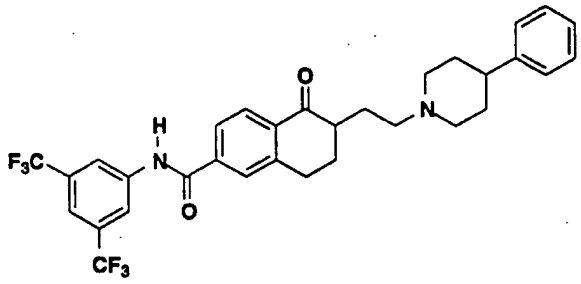
Anal. for: $C_{31}H_{34}N_2O_2 \cdot 0.93\ H_2O$:

Calc'd: C, 77.03; H, 7.48; N, 5.80.

Found: C, 77.02; H, 7.17; N, 5.72.

**Example 149**

**N-[3,5-Bis(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 212.0-216.0.

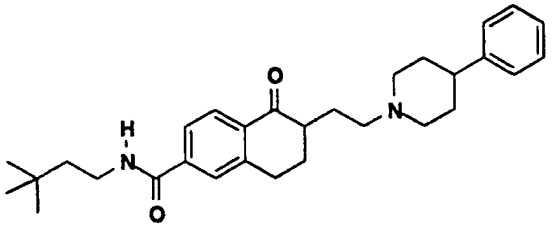
Anal. for: $C_{32}H_{30}F_6N_2O_2 \cdot HCl$:

Calc'd: C, 61.49; H, 5.00; N, 4.48.

Found: C, 61.21; H, 4.93; N, 4.42.

**Example 150**

**5,6,7,8-Tetrahydro-N-(3,3-dimethylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 266.0-270.0.

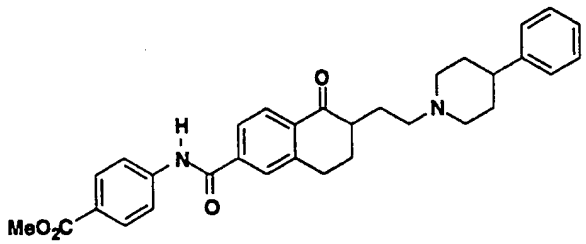
Anal. for: $C_{30}H_{40}N_2O_2 \cdot HCl \cdot 0.26\ H_2O$:

Calc'd: C, 71.81; H, 8.22; N, 5.56; Cl, 6.84.

Found: C, 71.81; H, 8.34; N, 5.58, Cl, 7.07.

**Example 151**

**4-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]benzoic acid, methyl ester**



mp (°C) 221.0-224.0.

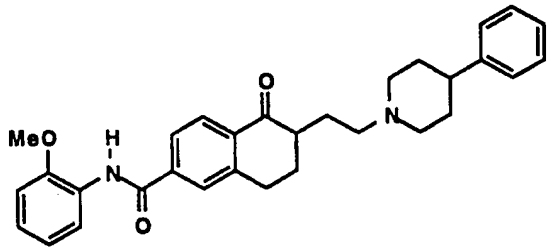
Anal. for: $C_{32}H_{34}N_2O_4 \cdot 0.44\ H_2O$:

Calc'd: C, 74.13; H, 6.78; N, 5.40.

Found: C, 74.13; H, 6.50; N, 5.41.

**Example 152**

**5,6,7,8-Tetrahydro-N-(2-methoxyphenyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 237.0-239.0.

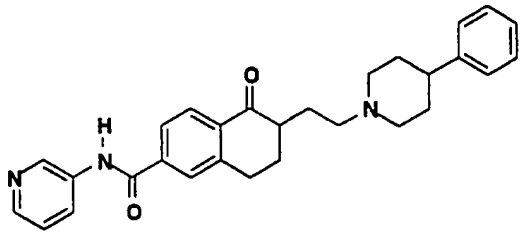
Anal. for: $C_{31}H_{34}N_2O_3 \cdot HCl \cdot 0.63\ H_2O$:

Calc'd: C, 70.19; H, 6.89; N, 5.28; Cl, 6.68.

Found: C, 70.19; H, 6.58; N, 5.25; Cl, 6.68.

**Example 153**

**5,6,7,8-Tetrahydro-N-(3-pyridinyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 273.0-277.0.

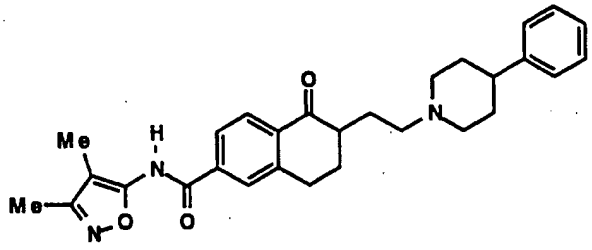
Anal. for: $C_{29}H_{31}N_3O_2 \cdot HCl \cdot 0.95\ H_2O$:

Calc'd: C, 68.68; H, 6.74; N, 8.29; Cl, 6.94.

Found: C, 68.68; H, 6.42; N, 8.21; Cl, 7.14.

**Example 154**

**5,6,7,8-Tetrahydro-N-(3,4-dimethyl-5-isoxazolyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 188.0-191.0.

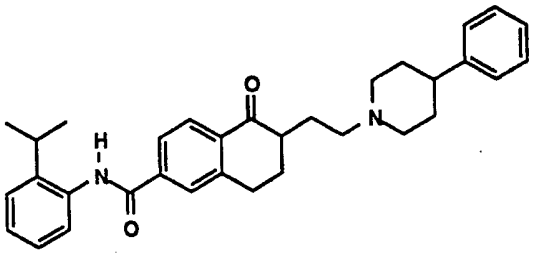
Anal. for: $C_{29}H_{33}N_3O_3 \cdot HCl \cdot 0.44\ H_2O$:

Calc'd: C, 67.50; H, 6.81; N, 8.14; Cl, 6.87.

Found: C, 67.50; H, 6.44; N, 7.99; Cl, 6.87.

**Example 155**

**5,6,7,8-Tetrahydro-N-[2-(1-methylethyl)phenyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:1.37) hydrochloride**



mp (°C) 213.0-215.0.

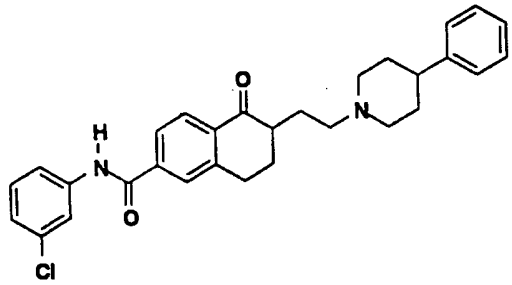
Anal. for: $C_{33}H_{38}N_2O_2 \cdot 1.37$ HCl:

Calc'd: C, 72.99; H, 7.28; N, 5.16; Cl, 8.94.

Found: C, 72.99; H, 7.34; N, 5.03; Cl, 9.31.

**Example 156**

**N-(3-Chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:2.07) hydrochloride**



mp (°C) 269.0-271.0.

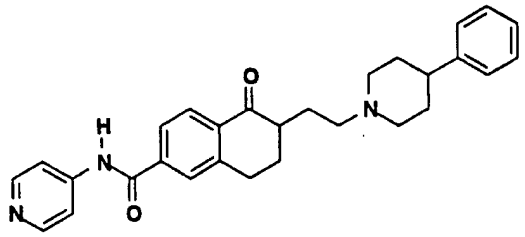
Anal. for: $C_{30}H_{31}ClN_2O_2 \cdot 2.07$ HCl $\cdot$ 0.36 $H_2O$

Calc'd: C, 63.32; H, 5.99; N, 4.92; Cl, 19.13.

Found: C, 63.32; H, 5.82; N, 4.81; Cl, 19.14.

**Example 157**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-pyridinyl)-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 245.0-248.0.

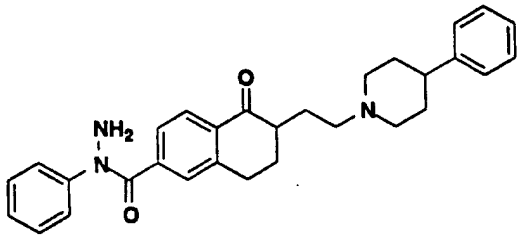
Anal. for: $C_{29}H_{31}N_3O_2 \cdot 1.12\ HCl \cdot 0.61\ H_2O$:

Calc'd: C, 68.92; H, 6.65; N, 8.31; Cl, 7.86.

Found: C, 68.92; H, 6.38; N, 8.23; Cl, 7.84.

**Example 158**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, 1-phenylhydrazide, dihydrochloride**



mp (°C) 163.0-166.0.

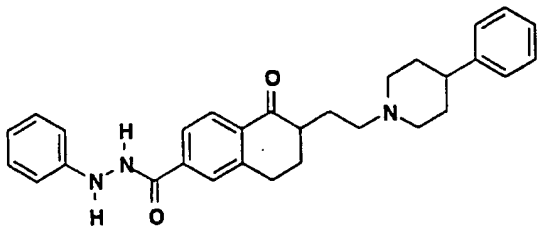
Anal. for: $C_{30}H_{33}N_3O_2 \cdot 2.06\ HCl \cdot 1.41\ H_2O$

Calc'd: C, 63.42; H, 6.72; N, 7.40; Cl, 12.85.

Found: C, 63.42; H, 6.34; N, 7.37; Cl, 12.86.

**Example 159**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-pyridinyl)-2-naphthalenecarboxylic acid, 2-phenylhydrazide, hydrochloride**



mp (°C) 262.0-265.0.

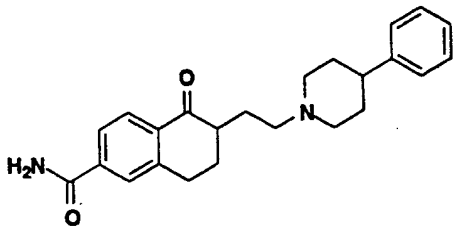
Anal. for: $C_{30}H_{33}N_3O_2 \cdot 1.25$ HCl:

Calc'd: C, 70.21; H, 6.73; N, 8.19.

Found: C, 70.21; H, 6.36; N, 7.96.

**Example 160**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 216.0-218.0.

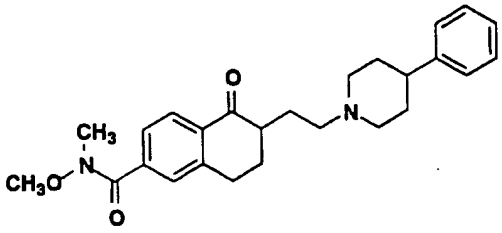
Anal. for: $C_{24}H_{28}N_2O_2$:

Calc'd: C, 76.56; H, 7.50; N, 7.44.

Found: C, 76.29; H, 7.47; N, 7.33

**Example 161**

**5,6,7,8-Tetrahydro-N-methoxy-N-methyl-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 82.5-85.0.

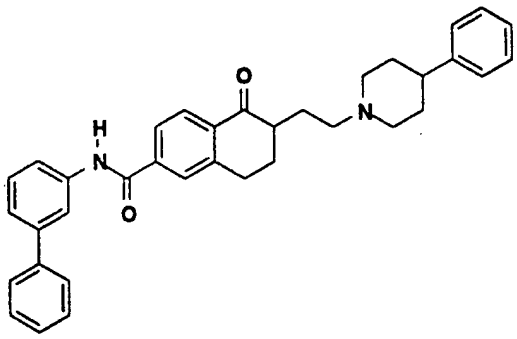
Anal. for: $C_{26}H_{32}N_2O_3 \cdot 0.12\ CH_2Cl_2$:

Calc'd: C, 72.82; H, 7.55; N, 6.50.

Found: C, 72.82; H, 7.43; N, 6.58.

**Example 162**

**N-([1,1-Biphenyl]-3-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 208.0-211.0.

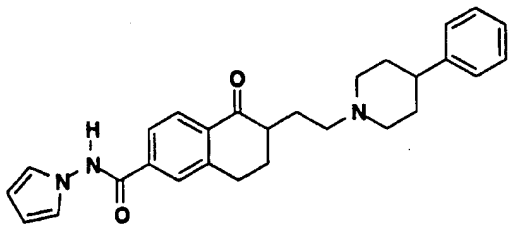
Anal. for: $C_{36}H_{36}N_2O_2 \cdot 1.23\ H_2O$:

Calc'd: C, 78.50; H, 7.04; N, 5.09.

Found: C, 78.39; H, 6.70; N, 5.49.

**Example 163**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(1H-pyrrol-1-yl)-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 284.0-288.0.

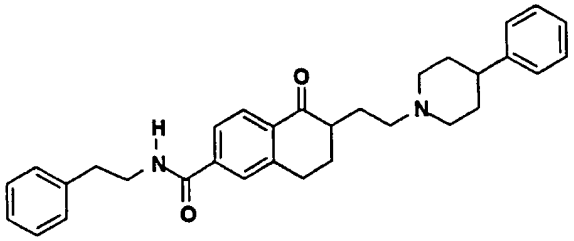
Anal. for: $C_{28}H_{31}N_3O_2 \cdot HCl \cdot 0.53\ H_2O$:

Calc'd: C, 68.97; H, 6.83; N, 8.65.

Found: C, 68.97; H, 6.51; N, 8.65.

**Example 164**

**5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 149.0-150.0.

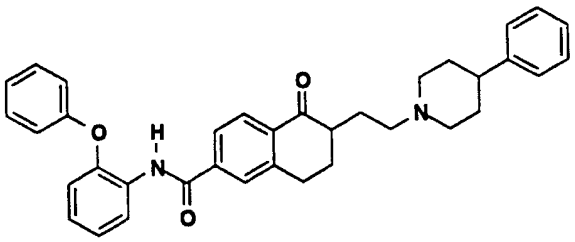
Anal. for: $C_{32}H_{36}N_2O_2 \cdot 1.50\ H_2O$:

Calc'd: C, 75.70; H, 7.74; N, 5.52.

Found: C, 75.40; H, 7.34; N, 5.78.

**Example 165**

**5,6,7,8-Tetrahydro-5-oxo-N-(2-phenoxyphenyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**



mp (°C) 234.0-236.5.

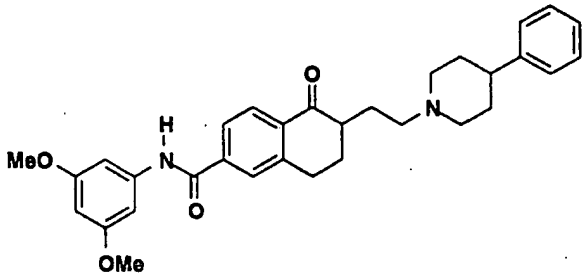
Anal. for: $C_{36}H_{36}N_2O_3 \cdot HCl$:

Calc'd: C, 74.40; H, 6.42; N, 4.82; Cl, 6.10.

Found: C, 74.18; H, 6.29; N, 4.73; Cl, 5.74.

**Example 166**

**N-(3,5-Dimethoxyhenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride**




mp (°C) 281.0-284.0.

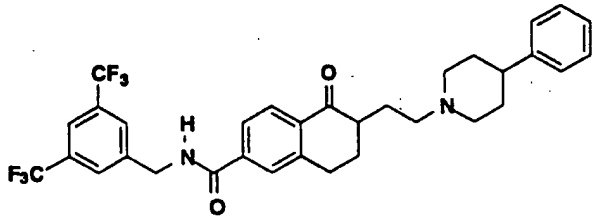
Anal. for: $C_{32}H_{36}N_2O_4 \cdot HCl \cdot 1.06\ H_2O$:

Calc'd: C, 67.64; H, 6.94; N, 4.93.

Found: C, 67.64; H, 6.60; N, 4.83.

**Example 167**

**N-(3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide, monohydrochloride**




mp (°C) 275.0-278.0.

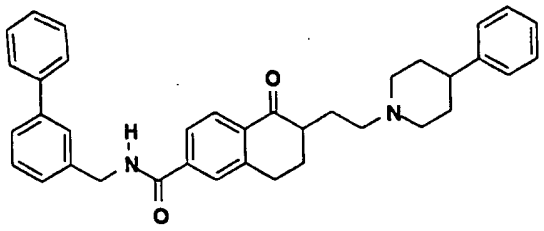
Anal. for: $C_{33}H_{32}F_6N_2O_2 \cdot HCl \cdot 0.55\ H_2O$:

Calc'd: C, 61.08; H, 5.30; N, 4.32; F, 17.57; Cl, 5.46.

Found: C, 61.08; H, 5.06; N, 4.36; F, 17.44; Cl, 5.69.

**Example 168**

**N-(1,1-Biphenyl]-2-ylmethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:1.07) hydrochloride**



mp (°C) 236.0-238.0.

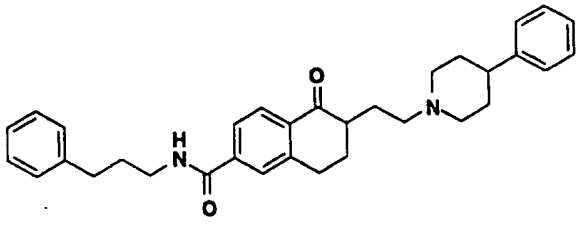
Anal. for: $C_{37}H_{38}N_2O_2 \cdot 1.07\ HCl \cdot 0.16\ H_2O$:

Calc'd: C, 76.01; H, 6.79; N, 4.79; Cl, 6.49.

Found: C, 76.01; H, 6.72; N, 4.72; Cl, 6.50.

**Example 169**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(3-phenylpropyl)-2-naphthalenecarboxamide**



mp (°C). 114.0-118.0.

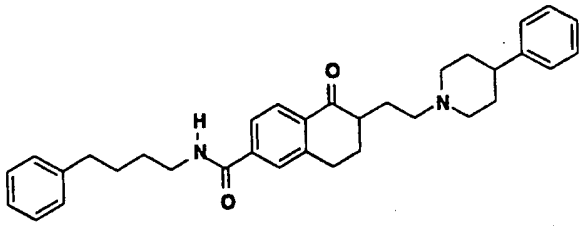
Anal. for: for $C_{33}H_{38}N_2O_2 \cdot 0.72\ H_2O$:

Calc'd: C, 78.02; H, 7.83; N, 5.51.

Found: C, 78.02; H, 7.67; N, 5.63.

**Example 170**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-phenylbutyl)-2-naphthalenecarboxamide**



mp (°C) 139.0-140.5.

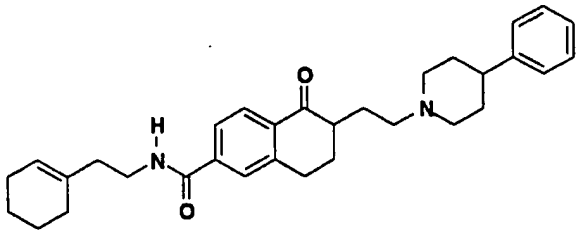
Anal. for: $C_{34}H_{40}N_2O_2 \cdot 0.76\ H_2O$.

Calc'd: C, 78.17; H, 8.01; N, 5.36.

Found: C, 78.17; H, 7.74; N, 5.46.

**Example 171**

**N-[2-Cyclohexen-1-yl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C). 144.0-146.0.

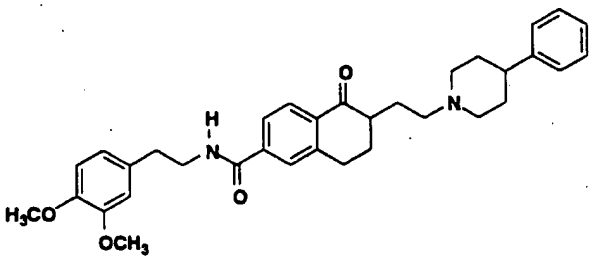
Anal. for: $C_{32}H_{40}N_2O_2 \cdot 0.41\ H_2O$:

Calc'd: C, 78.10; H, 8.36; N, 5.69.

Found: C, 78.10; H, 8.20; N, 5.71.

**Example 172**

**N-[2-(3,4-Dimethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 159.5-162.0.

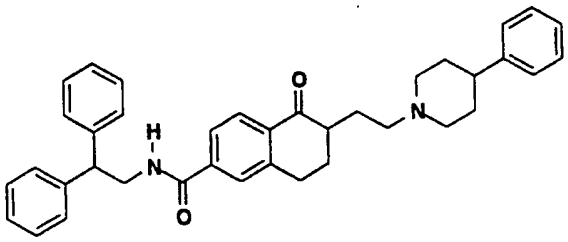
Anal. for: $C_{34}H_{40}N_2O_4 \cdot 0.90\ H_2O$:

Calc'd: C, 73.33; H, 7.57; N, 5.03.

Found: C, 73.33; H, 7.32; N, 5.04.

**Example 173**

**N-[2,2-Diphenylethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 158.0-161.0.

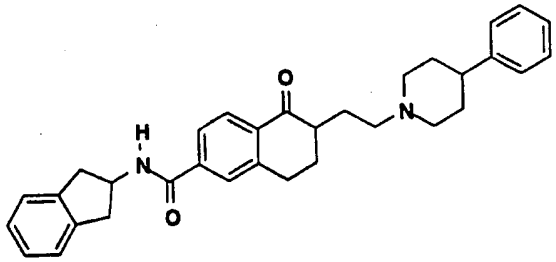
Anal. for: $C_{38}H_{40}N_2O_2 \cdot 0.67\ H_2O$:

Calc'd: C, 80.24; H, 7.33; N, 4.92.

Found: C, 80.24; H, 7.05; N, 4.87.

**Example 174**

**N-[2,3-Dihydro-1H-inden-2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 205.0-208.0.

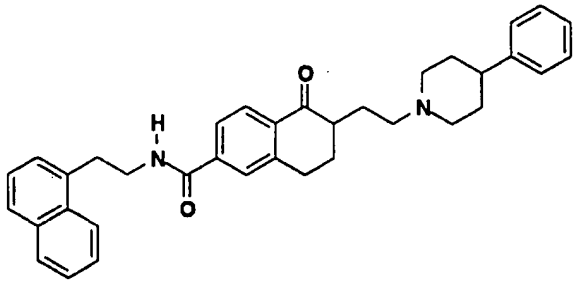
Anal. for: $C_{33}H_{36}N_2O_2 \cdot 0.74\ H_2O$:

Calc'd: C, 78.34; H, 7.47; N, 5.54.

Found: C, 78.34; H, 7.21; N, 5.52.

**Example 175**

**5,6,7,8-Tetrahydro-N-[2-(1-naphthalenyl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, hydrochloride**



mp (°C) 45.0-50.0.

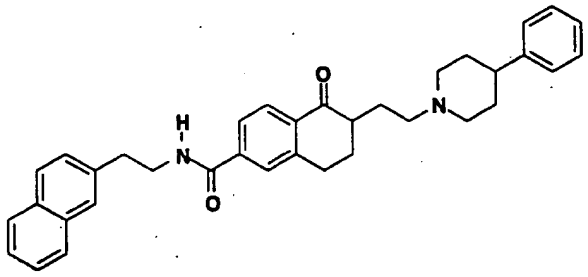
Anal. for: $C_{36}H_{38}N_2O_2 \cdot 0.88$ Hcl:

Calc'd: C, 76.82; H, 6.96; N, 4.98.

Found: C, 76.82; H, 6.99; N, 4.82.

**Example 176**

**5,6,7,8-Tetrahydro-N-[2-(2-naphthalenyl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 176.0-178.0.

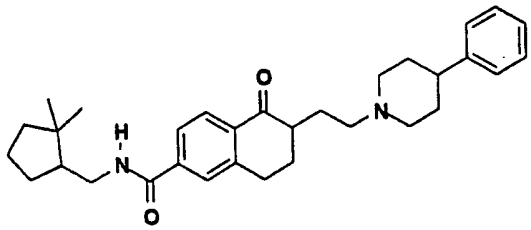
Anal. for: $C_{36}H_{38}N_2O_2 \cdot 0.34\ H_2O$:

Calc'd: C, 80.54; H, 7.26; N, 5.22.

Found: C, 80.54; H, 7.12; N, 5.26.

**Example 177**

**N-[(2,2-Dimethylcyclopentyl)methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



Anal. for: $C_{32}H_{42}N_2O_2 \bullet 0.96\ H_2O$:

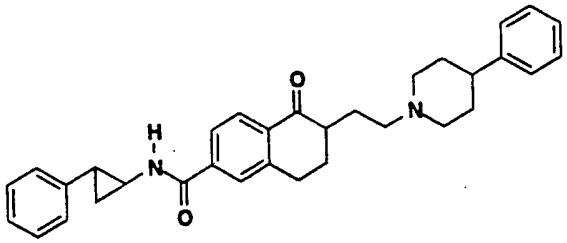
Calc'd: C, 76.25; H, 8.78; N, 5.56.

Found: C, 76.25; H, 8.26; N, 5.29.

oil

**Example 178**

**trans-5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylcyclopropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 72.0-78.0.

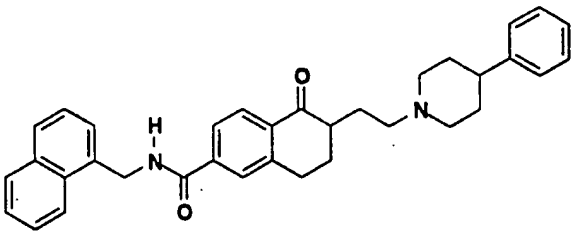
Anal. for: $C_{33}H_{36}N_2O_2 \bullet 0.44\ H_2O$:

Calc'd: C, 79.17; H, 7.43; N, 5.60.

Found: C, 79.17; H, 7.20; N, 5.49.

**Example 179**

**5,6,7,8-Tetrahydro-N-(1-naphthalenylmethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



mp (°C) 88.0-92.0.

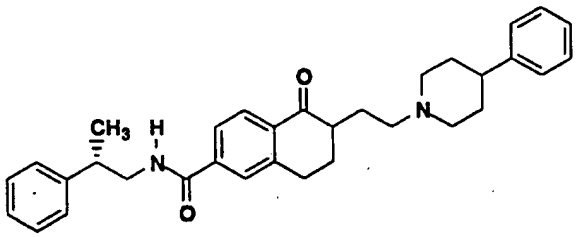
Anal. for: $C_{35}H_{36}N_2O_2 \bullet 0.39\ H_2O$:

Calc'd: C, 80.26; H, 7.08; N, 5.35.

Found: C, 80.26; H, 6.75; N, 5.14.

**Example 180**

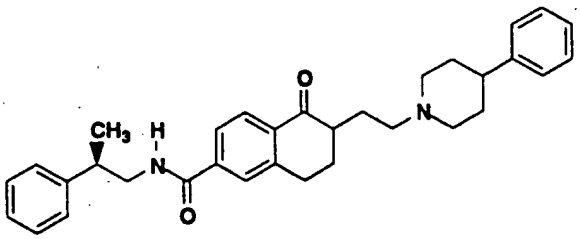
**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(S)-2-phenylcyclopropyl)-2-naphthalenecarboxamide**



495 M+1.

**Example 181**

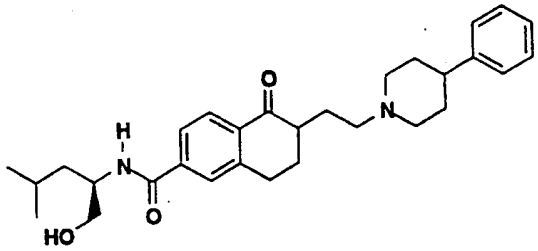
**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(R)-2-phenylcyclopropyl)-2-naphthalenecarboxamide**



495 M+1.

**Example 182**

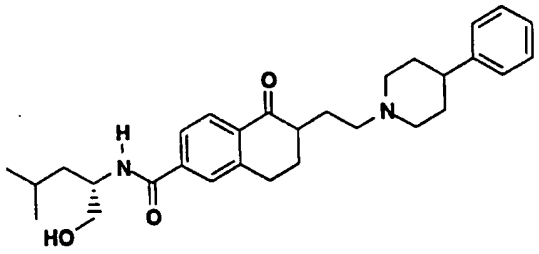
**5,6,7,8-Tetrahydro-N-[(R)-1-(hydroxymethyl)-3-methylbutyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide**



477 M+1.

**Example 183**

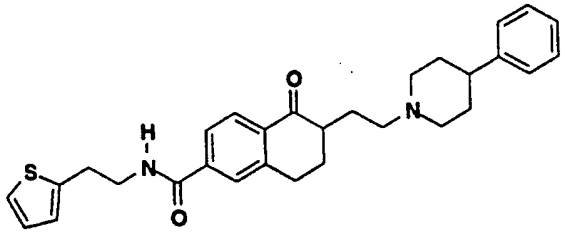
**5,6,7,8-Tetrahydro-N-[(S)-1-(hydroxymethyl)-3-methylbutyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide**



477 M+1.

**Example 184**

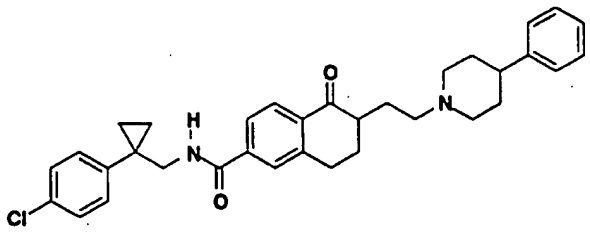
**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[2-(2-thienyl)ethyl]-2-naphthalenecarboxamide**



487 M+1.

**Example 185**

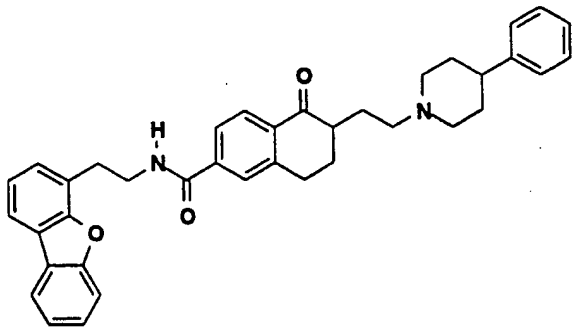
**N-[(1-(4-Chlorophenyl)cyclopropyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide**



541 M+1.

**Example 186**

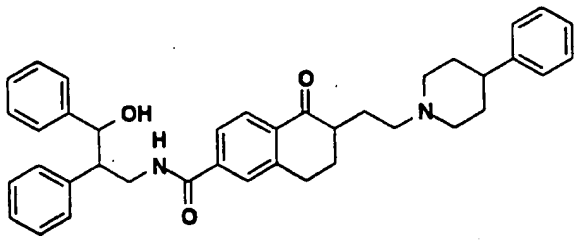
**N-[2-(4-Dibenzofuranyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



571 M+1.

**Example 187**

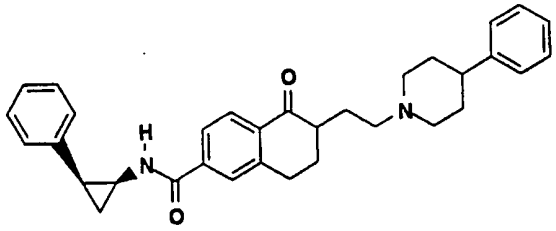
**5,6,7,8-Tetrahydro-N-(3-hydroxy-2,3-diphenylpropyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



587 M+1.

**Example 188**

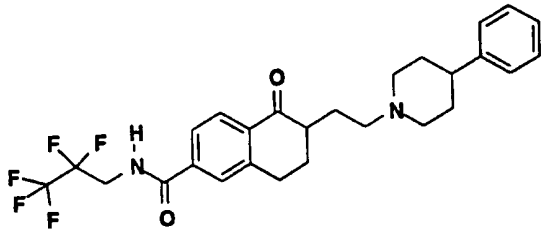
**cis-5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylcyclopropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



493 M+1.

**Example 189**

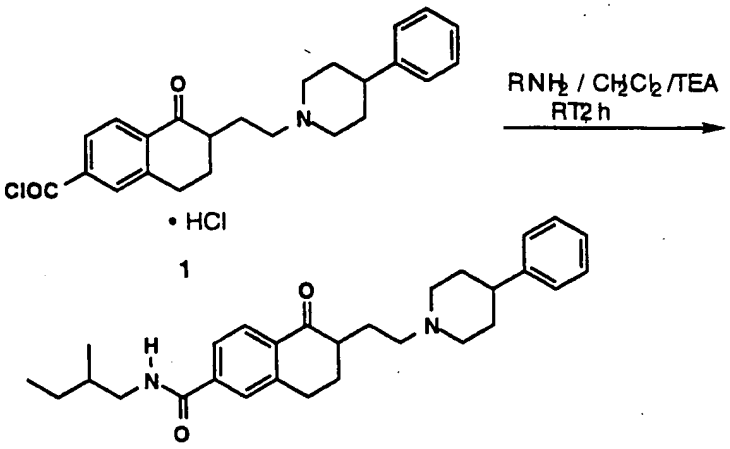
**5,6,7,8-Tetrahydro-5-oxo-N-(2,2,3,3,3-pentafluoropropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**



509 M+1.

**Example 190**

**5,6,7,8-Tetrahydro-N-(2-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**



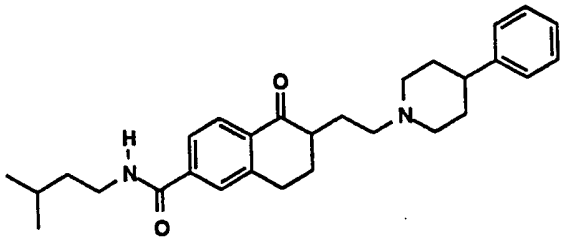

A solution of 1 (48 mg, 0.11 mmol), see Example 145 for reparation and triethylamine (0.018 mL, 0.13 mmol in $CH_2Cl_2$ (1 mL) was added to (2-methylbutyl)amine (0.07 mol). After shaking for 2 hours, the reaction was diluted with 5% MeOH/$CH_2Cl_2$ (1 mL) and the mixture was loaded onto a SAX column (6 g, pretreated with 20 mL 1N NaOAc, 40 mL $H_2O$, 20 mL MeOH, 20 mL $CH_2Cl_2$ and 10 mL 5% MeOH/$CH_2Cl_2$). The column was then eluted with 3 mL of 5% MeOH/$CH_2Cl_2$. The total effluent was collected and evaporated. The product was dissolved in 2 to 4 mL of 80% MeOH/$H_2O$ and then added in 2 mL portions to a preparative HPLC (YMS S5 ODS, 30 x 250 mm C-18, 25 mL/minute, 50% to 90% MeOH/$H_2O$ with 0.1% TFA linear gradient over 20 minutes, 5-minutes hold at 90%, detection at 217 nm). Fractions which were pure were combined and evaporated.

M+1: 447.

**Using methodology analogous to that described for the title compound of Example 190, the compounds of Examples 190a to 201 were prepared:**

**Example 190a**

**5,6,7,8-Tetrahydro-N-(3-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**

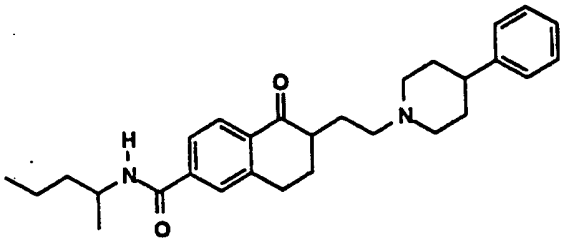


Yield 56%.

MS (ESI) 447.

**Example 191**

**5,6,7,8-Tetrahydro-N-(1-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**

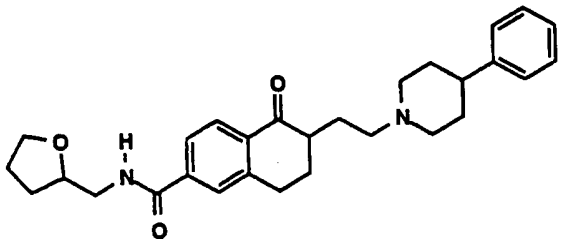


Yield 45%.

MS (ESI) 447.

**Example 192**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(tetrahydro-2-furanyl)methyl]-2-naphthalenecarboxamide, trifluoroacetate**

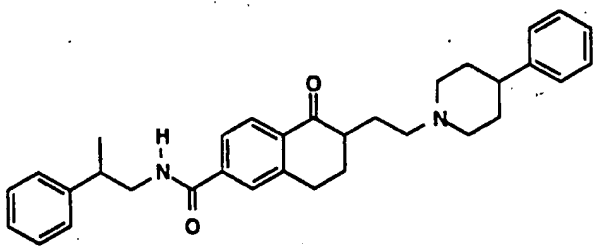


Yield 73%.

MS (ESI) 461.

**Example 193**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(2-phenylpropyl)-2-naphthalenecarboxamide, trifluoroacetate**

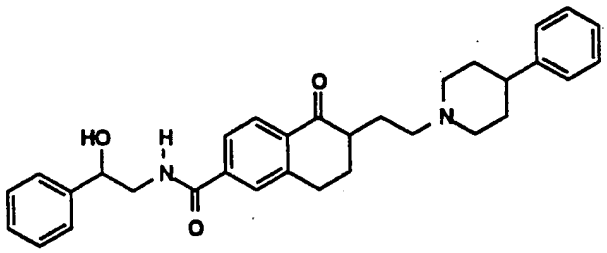


Yield 43%.

MS (ESI) 495.

**Example 194**

**5,6,7,8-Tetrahydro-N-(2-hydroxy-2-phenylethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**

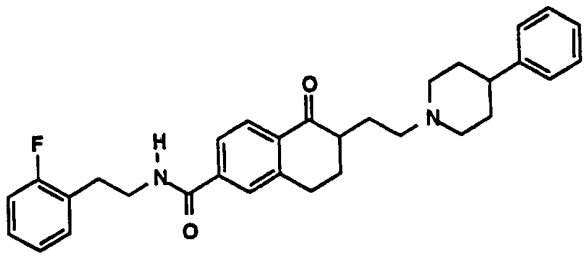


Yield 55%.

MS (ESI) 497.

**Example 195**

**N-[2-(2-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**

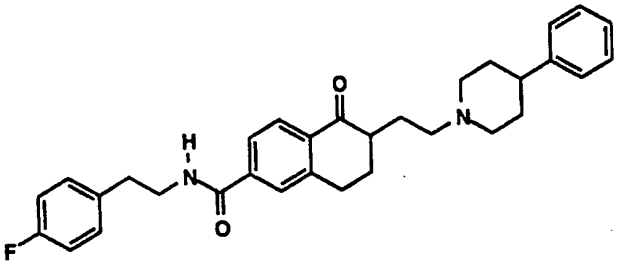


Yield 46%.

MS (ESI) 499.

**Example 196**

**N-[2-(4-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-6-naphthalenecarboxamide, trifluoroacetate**

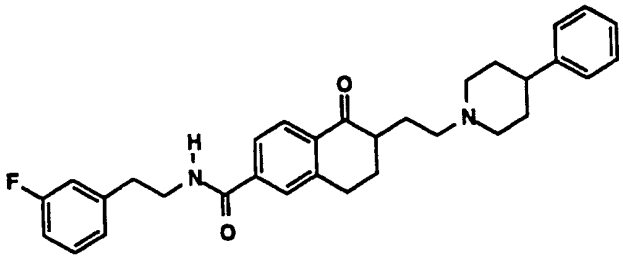


Yield 42%.

MS (ESI) 499.

**Example 197**

**N-[2-(3-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**

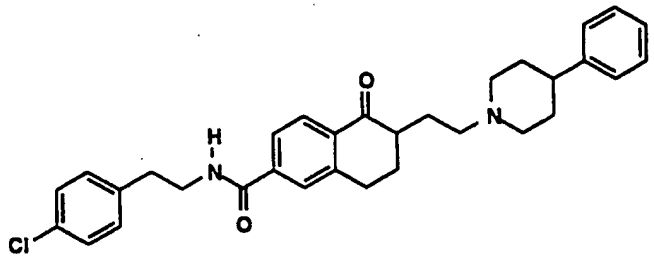


Yield 54%.

MS (ESI) 499.

**Example 198**

**N-[2-(4-Chlorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**

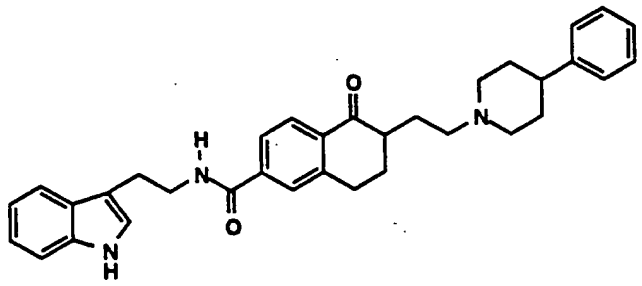


Yield 51%.

MS (ESI) 516.

**Example 199**

**5,6,7,8-Tetrahydro-N-[2-(1H-indol-3-yl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**

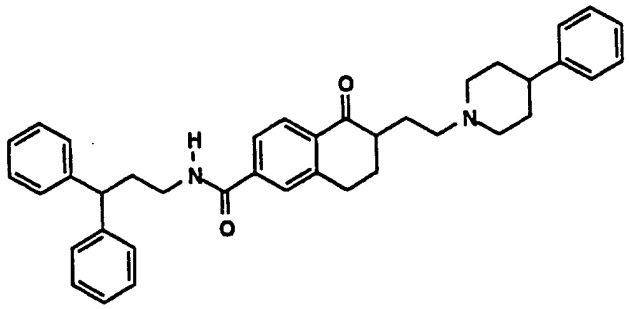


Yield 37%.

MS (ESI) 520.

**Example 200**

**N-(3,3-Diphenylpropyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**

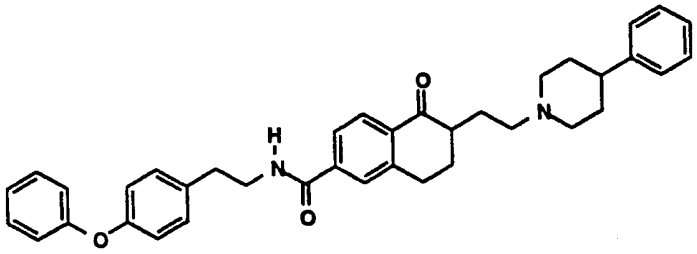


Yield 41%.

MS (ESI) 571.

**Example 201**

**5,6,7,8-Tetrahydro-5-oxo-N-[2-(4-phenoxyphenyl)ethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**

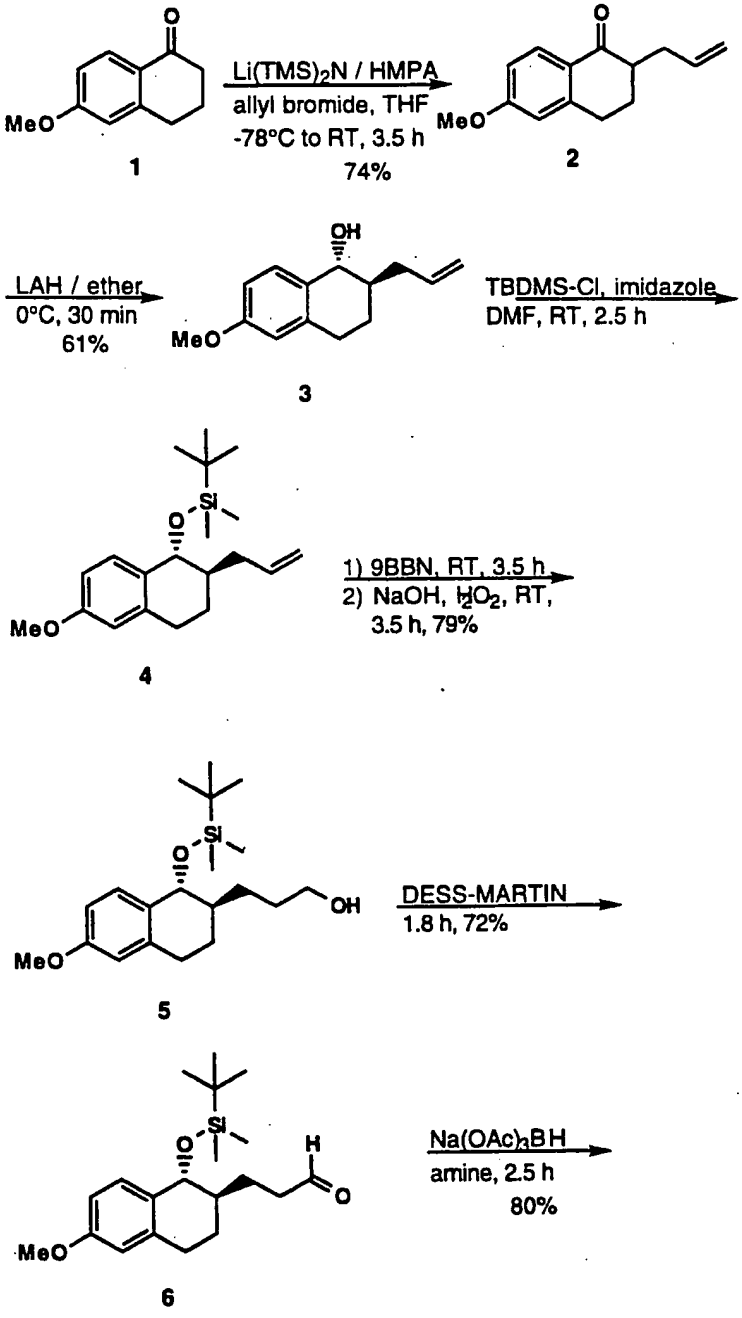


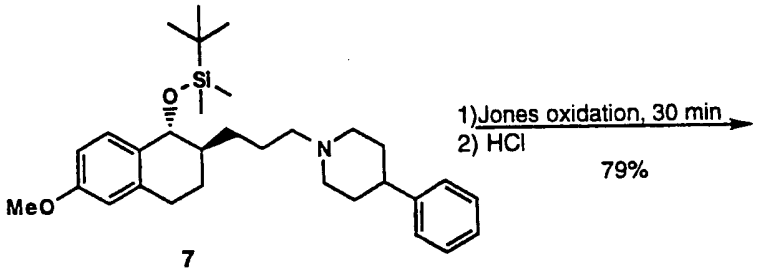
Yield 28%.

MS (ESI) 573.

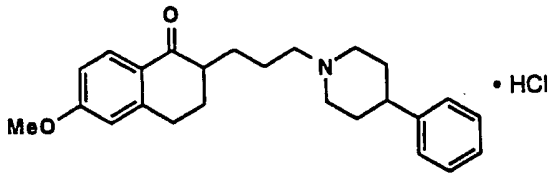
**Example 202**

**3,4-Dihydro-6-methoxy-2-[3-(4-phenyl-1-piperidinyl)propyl]-1(2H)-naphthalenone, monohydrochloride**


MeO
1
Li(TMS)2N / HMPA
allyl bromide, THF
-78°C to RT, 3.5 h
74%
2
LAH / ether
0°C, 30 min
61%
3
TBDMS-Cl, imidazole
DMF, RT, 2.5 h
4
1) 9BBN, RT, 3.5 h
2) NaOH, H2O2, RT,
3.5 h, 79%
5
DESS-MARTIN
1.8 h, 72%
6
Na(OAc)3BH
amine, 2.5 h
80%




7




A. **3,4-Dihydro-6-methoxy-2-(1-prop-2-enyl)-1(2H)-naphthalenone**

A solution of 6-methoxy-1-tetralone (0.88 g, 5.0 mmol) in THF (25 mL) was stirred in an oven-dried flask at -78°C under argon. Lithium hexamethyldisilamide (1 M in THF, 5.2 mL, 5.2 mmol) was slowly added over 10 minutes. After stirring at -78°C for 15 minutes, HMPA (1.8 g, 1.7 mL, 10 mmol) was added. After stirring an additional 5 minutes at -78°C, allyl bromide (0.60 g, 0.43 mL, 5.0 mmol) in THF (5 mL) was added slowly over 10 minutes. The cold bath was then removed and the reaction allowed to slowly warm to room temperature over 3.5 hours. The reaction was quenched by adding 1 N HCl and transferred to a separatory funnel with $CH_2Cl_2$ and 1 N HCl. Extraction with $CH_2Cl_2$ (2 x 100 mL), washing the combined organic layers with water, and drying over $MgSO_4$ afforded 2.2 g of crude product after evaporation of the solvent. Flash chromatography (silica, 50 mm dia, 15% EtOAc/hexane) afforded 0.80 g (74%) of the title compound: $R_f$ (silica, 40% EtOAc/hexane) = 0.55.

**B. trans-1,2,3,4-Tetrahydro-6-methoxy-2-(1-prop-2-enyl)-1-naphthalenol**

Lithium aluminum hydride (1 M in ether, 8.3 mL, 8.3 mmol) was added to ether (8.3 mL) stirring a 0°C under argon in a flame dried flask. A solution of the title A compound (3.4 g, 16 mmol) in ether (5 mL) was added over 5 minutes. After stirring at 0°C for 30 minutes, the reaction was quenched with saturated $NH_4Cl$ and transferred to a separatory funnel with water/ether. Extraction with ether (2 x 250 mL), washing the combined organic layers with brine, and drying over $MgSO_4$ afforded 3.9 g of crude product. Flash chromatography (silica gel, 10% EtOAc/hexane) afforded 1.92 g of the title compound: mp 63.0-65.0°C; $R_f$ (silica gel, 25% EtOAc/hexane) = 0.25.

**C. Compound 4.**

t-butyldimethylsilyl chloride (3.1 g, 20 mmol) was added to a solution of title B compound (0.90 g, 4.1 mmol) and imidazole (2.8 g, 41 mmol) in DMF (3.3 mL) stirring under argon. After stirring at ambient temperature for 2.5 hours, the reaction solution was transferred to a separatory funnel with water/ether (pH of the aqueous layer was 8). Extraction with ether (2 x 70 mL), washing the combined organic layers with water and brine, and drying over $MgSO_4$ afforded 3.5 g of crude product after evaporation of the solvent. Flash chromatography (silica gel, 5% EtOAc/hexane) afforded 1.7 g (>100%) of compound 4.

**D. Compound 5.**

A solution of the title C compound (1.8 g, 4.6 mmol) in THF (4.5 mL) was added to 9-BBN (0.5 M in THF, 13 mL, 6.4 mmol) stirring in a flame dried flask under argon. After stirring at ambient temperature for 3.5 hours, the reaction was quenched with water (0.45 mL). 2N NaOH (4.5 mL) and then hydrogen peroxide (30% solution, 2.3 mL) were added. After stirring for 3.5 hours, the reaction was quenched with

saturated $NaHCO_3$ solution and transferred to a separatory funnel with water/$CH_2Cl_2$. Extraction with $CH_2Cl_2$ (3 x 30 mL) and drying over $MgSO_4$ afforded 2.0 g of crude product. Flash chromatography (silica gel, 20% EtOAc/hexane) afforded 1.3 g (79%) of the title compound.

**E. Compound 6.**

Dess-Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, 3.0 g, 4.8 mmol) was added to a solution of the title D compound 3 (1.1 g, 3.2 mmol) in $CH_2Cl_2$ (20 mL) stirring under argon at ambient temperature in a flame-dried flask. After stirring at ambient temperature for 1.8 hours, ether was added and the reaction evaporated *in vacuo* . The residue was transferred to a separatory funnel with ether (200 mL) and 1/1 10% $Na_2S_2O_3$/saturated $NaHCO_3$ (150 mL). Extraction with ether and washing with water (50 mL) and brine (50 mL) and drying over $MgSO_4$ afforded 1.1 g of crude product. Flash chromatography (silica gel, 10% EtOAc/hexane) afforded 0.80 g (72%) yield of compound 6: $R_f$ (silica, 15% EtOAc/hexane) = 0.45.

**F. Compound 7.**

Sodium triacetoxyborohydride (0.68 g, 3.2 mmol) was added to a solution of 4-phenylpiperidine (0.45 g, 2.8 mmol), aldehyde 6 (0.80 g, 2.3 mmol), and acetic acid (0.12 mL, 2.3 mmol) in THF (23 mL) stirring at ambient temperature under argon. After stirring for 2.5 hours, the solvent was removed *in vacuo*. The residue was transferred to a separatory funnel with EtOAc/saturated $NaHCO_3$. Extraction with EtOAc (2 x 80 mL), washing the combined organic layers with brine, and drying over $MgSO_4$ afforded 1.1 g of crude product after evaporation of the solvent. Flash chromatography (silica gel, 50% EtOAc/$CH_2Cl_2$) afforded 0.91 g (80%) of compound 7.

**G. 3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)propyl]-1(2H)-naphthalenone, monohydrochloride**

Jones reagent (1.25 M, 8.2 mL, 10.5 mmol) was added in 2 mL fractions over 1 hour to a solution of title F compound (0.91 g, 1.8 mmol) in acetone (40 mL) stirring at 0°C. The cold bath was then removed and the solution stirred at ambient temperature. After stirring for 30 minutes, the reaction was quenched with isopropanol (13 mL) and evaporated *in vacuo*. The residue was transferred to a separatory funnel with $CH_2Cl_2$ and 2N NaOH. Extraction with $CH_2Cl_2$ (2 x 100 mL) and drying over $MgSO_4$ afforded 1.4 g of crude product after evaporation of the solvent. Flash chromatography (silica, 5% MeOH/$CH_2Cl_2$) afforded 0.55 g (79%) of the desired product. This material was dissolved in $CH_2Cl_2$ (10 mL) and 4N HCl in dioxane (0.36 mL, 1.5 mmol) was added. After evaporating the solvent, the resulting solid was triturated with EtOAc and the solid collected to afford 0.61 g of the title compound: mp 209.0-212.0°C.

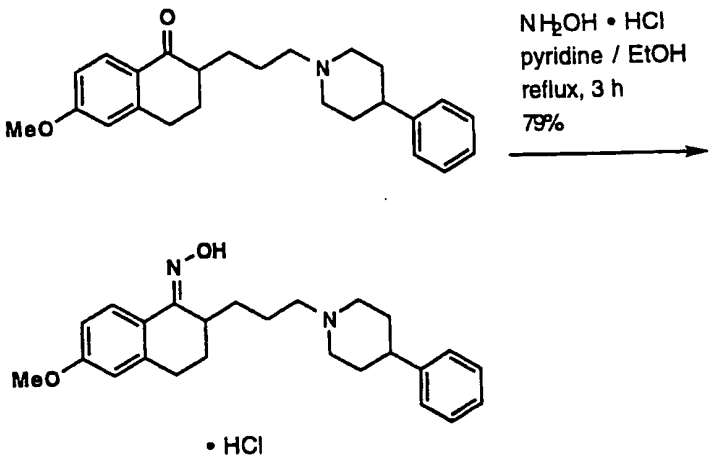
Anal. for: $C_{25}H_{31}NO_2 \cdot HCl \cdot 0.09\ CH_2Cl_2 \cdot 0.30\ H_2O$:

Calc'd: C, 70.56; H, 7.74; N, 3.28; Cl, 9.81.

Found: C, 70.59; H, 7.69; N, 3.16; Cl, 9.82.

**Example 203**

**(E)-3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)propyl]-1(2H)-naphthalenone, oxime**




Pyridine (1.3 mL, 17 mmol) was added to a stirring solution of the title compound of Example 202 (0.43 g, 1.0 mmol) and hydroxylamine hydrochloride (1.3 g, 19 mmol) in ethanol (24 mL). After refluxing for 3 hours, the reaction was cooled and the solvent evaporated *in vacuo*. The residue was transferred to a separatory funnel with EtOAc/sat. $NaHCO_3$. After extraction with EtOAc (2 x 120 mL), some solid remained suspended in the EtOAc. The combined EtOAc extracts were heated until everything was in solution and then filtered through a sintered glass funnel containing $MgSO_4$ rinsing with hot EtOAc (100 mL). The filtrate was evaporated to 150 mL and allowed to sit at ambient temperature overnight. The solid which crystallized was collected to afford 0.31 g (79%) of the title compound as a white solid. mp 209.0-211.5°C.

Anal. for: $C_{25}H_{32}N_2O_2 \cdot 0.31\ H_2O$:

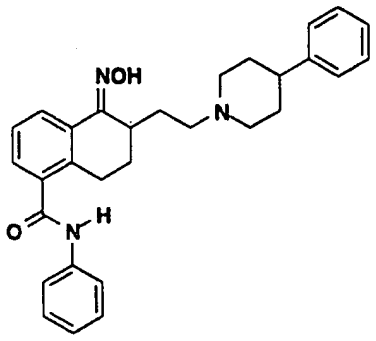
Calc'd: C, 70.41; H, 8.26; N, 7.03.

Found: C, 70.40; H, 8.43; N, 7.04.

**Using methodology analogous to that described for the title compound of Example 203, the compounds of Examples 204 to 208 were prepared:**

**Example 204**

**5,6,7,8-Tetrahydro-5-(hydroxyimino)-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**




mp (°C) 222.0-223.0.

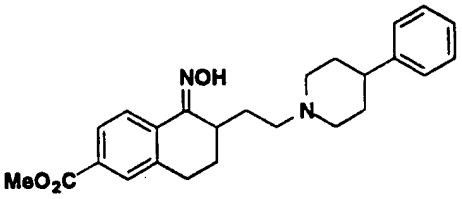
Anal. for: $C_{30}H_{33}N_3O_2 \cdot 0.20\ C_4H_8O_2 \cdot 0.70\ H_2O$:

Calc'd: C, 74.30; H, 7.29; N, 8.44.

Found: C, 74.30; H, 6.97; N, 8.35.

**Example 205**

**5,6,7,8-Tetrahydro-5-(hydroxyimino)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, methyl ester**




mp (°C) 189.5-191.

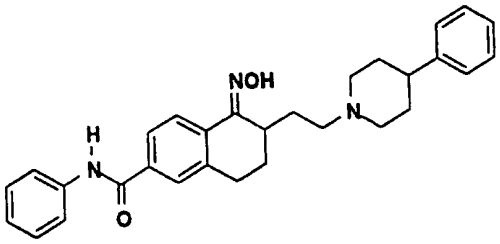
Anal. for: $C_{25}H_{30}N_2O_3 \cdot 0.08\ H_2O$

Calc'd: C, 73.59; H, 7.45; N, 6.87.

Found: C, 73.58; H, 7.26; N, 6.84.

**Example 206**

**5,6,7,8-Tetrahydro-5-(hydroxyimino)-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**




mp (°C) 224.0-226.5.

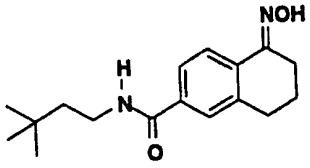
Anal. for: $C_{30}H_{33}N_3O_2 \cdot 0.32\ H_2O$:

Calc'd: C, 76.12; H, 7.16; N, 8.88.

Found: C, 76.12; H, 7.01; N, 6.82.

**Example 207**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-naphthalenecarboxamide**




mp (°C) 183.5-185.5.

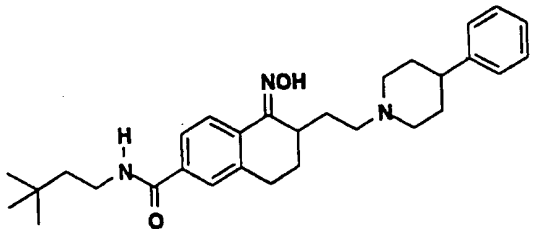
Anal. for: $C_{17}H_{24}N_2O_2$:

Calc'd: C, 70.80; H, 8.39; N, 9.71.

Found: C, 70.63; H, 8.54; N, 9.62.

**Example 208**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-(hydroxyimino)-6-[2-(4-phenyl)-1-piperidinyl)ethyl]-2-naphthalenecarboxamide**




mp (°C) 218.0-220.0.

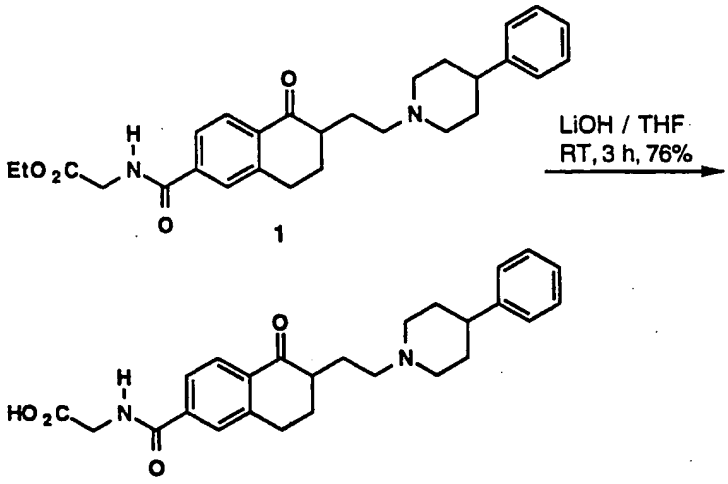
Anal. for: $C_{30}H_{41}N_3O_2 \cdot 0.34$ HCl:

Calc'd: C, 74.80; H, 8.72; N, 8.72.

Found: C, 74.80; H, 8.58; N, 8.65.

**Example 209**

**2-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]acetic acid**




Lithium hydroxide (1 M, 0.45 mL, 0.45 mmol) was added to a solution of ester compound 1 (the title compound of Example 142) (200 mg, 0.39 mmol) in THF (4 mL). After stirring at ambient temperature for 3 hours, the solvent was evaporated *in vacuo*. Chromatography of the residue (HP-20, 15 mm dia, 0% to 60% acetone/$H_2O$ in 10% increments of 50 mL each) afforded 0.14 g (76%) of the title compound after lyophilization. mp (°C) 152.0-156.0.

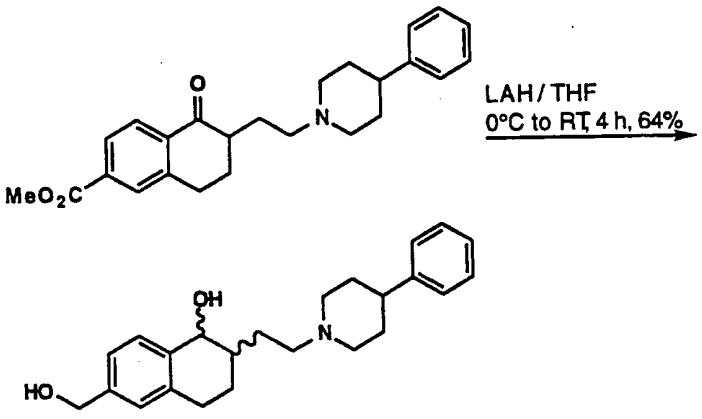
Anal. for: $C_{26}H_{30}N_2O_4 \cdot 1.20\ H_2O$:

Calc'd: C, 68.46; H, 7.16; N, 6.14.

Found: C, 68.48; H, 7.09; N, 5.94.

**Example 210**

**1,2,3,4-Tetrahydro-6-(hydroxymethyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol**




Lithium aluminum hydride (0.16 g, 4.0 mmol) in THF (3.9 mL) was stirred at 0°C in a flame dried flask under argon. The title C compound of Example 138a (0.50 g, 1.3 mmol) in THF (7.8 mL) was added and the reaction stirred a 0°C for 2 hours. After stirring at ambient temperature for an additional 2 hours, water (10 drops) was added to the reaction and then $Na_2SO_4 \cdot 10\ H_2O$ (120 mg) was added. Water was added dropwise with vigorous stirring until the precipitate was granular. Anhydrous $Na_2SO_4$ was added and the solid filtered rinsing with THF. The filtrate was evaporated, dissolved in $CH_2Cl_2$, and dried over $MgSO_4$ to afford 0.56 g of crude product. Flash chromatography (alumina-Activity III, 75% to 90% EtOAc/$CH_2Cl_2$ and flushed with 5% MeOH/EtOAc) afforded 0.30 g (64%) of the title compound. mp (°C) 131.0-134.5.

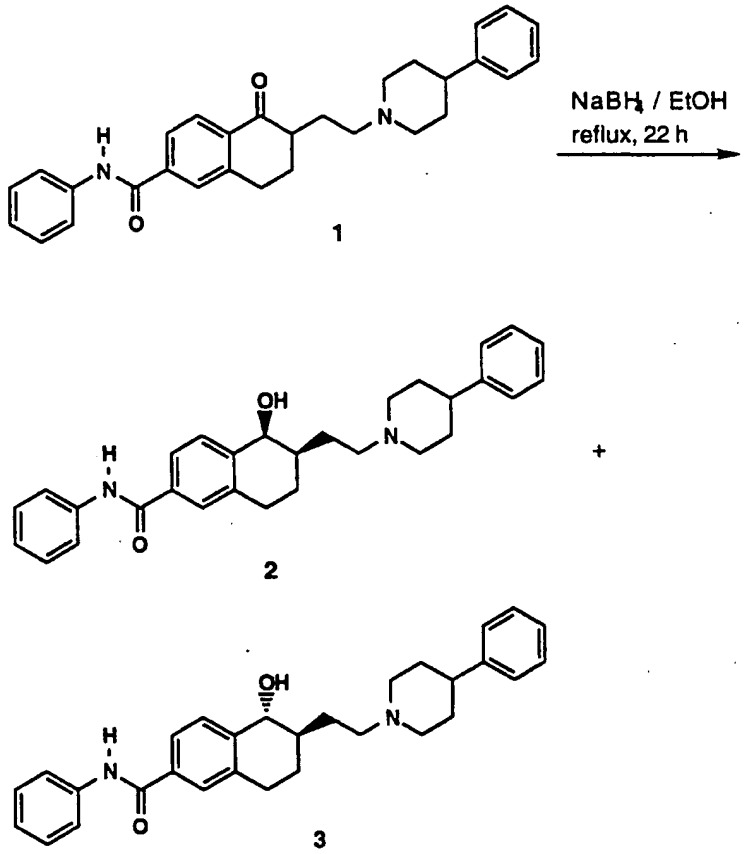
Anal. for: $C_{24}H_{31}NO_2 \cdot 0.29\ H_2O$:

Calc'd: C, 77.76; H, 8.59; N, 3.78.

Found: C, 77.76; H, 8.43; N, 3.73.

**Example 211**

**cis-5,6,7,8-Tetrahydro-5-hydroxy-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate**




Sodium borohydride (55 mg, 1.5 mmol) was added to a solution of the title compound of Example 138a (0.55 g, 1.2 mmol) in EtOH (18 mL). After refluxing for 22 hours, the reaction was cooled and transferred to a separatory funnel with $CH_2Cl_2/H_2O$. The pH was adjusted to 8.5. Extraction with $CH_2Cl_2$ (2 x 80 mL) and drying over $MgSO_4$ afforded 0.60 g of crude product after evaporation of the solvent. Preparative HPLC afforded 17 mg (2%) of compound 2 after evaporation *in vacuo* and lypholization: mp (°C) 221.0-222.0.

Anal. for: $C_{30}H_{34}N_2O_2 \cdot 1.16\ C_2HF_3O_2$:

Calc'd: C, 66.03; H, 6.05; N, 4.76.

Found: C, 66.03; H, 6.10; N, 4.83.

Further elution afforded 209 mg (28%) of compound 3. mp (°C) 231.0-233.5.

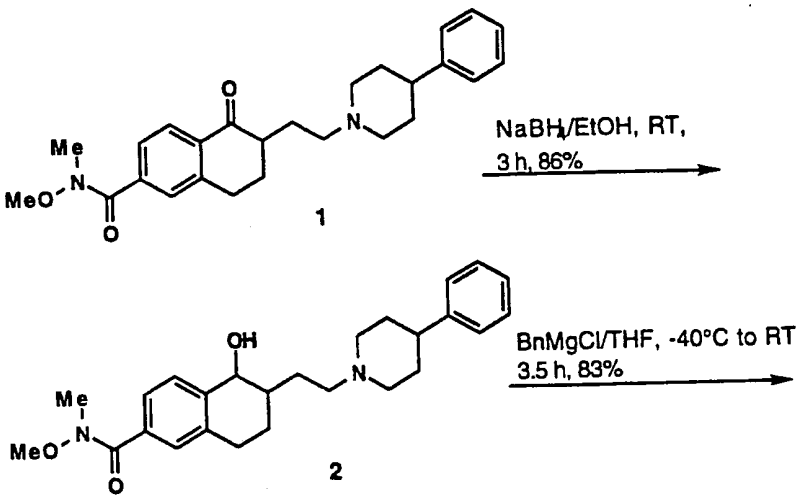
Anal. for: $C_{30}H_{34}N_2O_2 \cdot 1.35\ C_2HF_3O_2$:

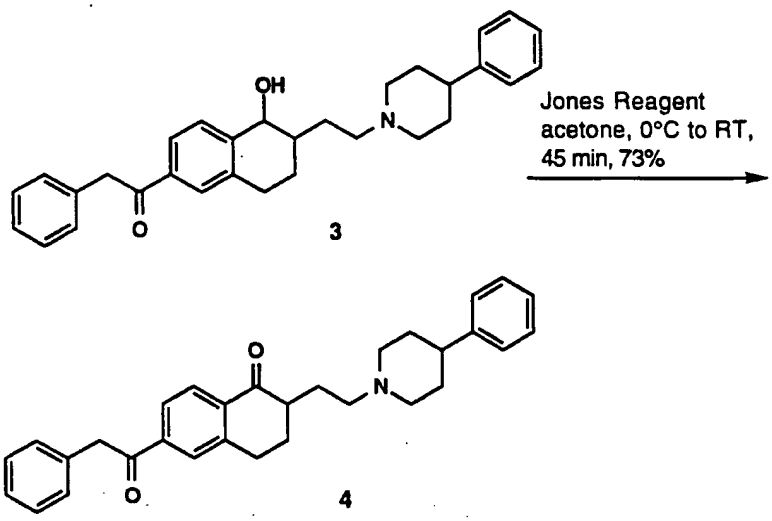
Calc'd: C, 64.51; H, 5.86; N, 4.60.

Found: C, 64.51; H, 5.73; N, 4.61.

**Example 212**

**3,4-Dihydro-6-(phenylacetyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**






**A. 5,6,7,8-Tetrahydro-5-hydroxy-N-methoxy-N-methyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide**

Sodium borohydride (77 mg, 2.1 mmol) was added to a solution of compound of Example 161 (0.88 g, 2.1 mmol) in ethanol (23 mL) stirring at ambient temperature. After stirring at ambient temperature for 3 hours, the reaction was quenched with $H_2O$ and transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer acidified with 1 N HCl and then basified to pH 8 with saturated $NaHCO_3$. Extraction with $CH_2Cl_2$ (2 x 40 mL) and drying over $MgSO_4$ afforded 0.99 g of crude product after evaporation of the solvent. Flash chromatography (silica gel, 5% MeOH/$CH_2Cl_2$) afforded 0.76 g (86%) of the title compound. $R_f$ (silica, 10% MeOH/$CH_2Cl_2$) = 0.17.

**B. 1-[5,6,7,8-Tetrahydro-5-hydroxy-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]-2-phenylethanone**

Benzylmagnesium chloride (2 M in THF, 0.68 mL, 1.4 mmol) was added to a solution of the title A compound (0.28 g, 0.66 mmol) in THF (7 mL) stirring at -40°C. The cold bath was removed and the reaction was

allowed to stir at ambient temperature. HPLC showed the reaction to be about half complete after 2.5 hours whereupon the reaction was cooled to -40°C and an additional 0.68 mL (1.4 mmol) of benzylmagnesium chloride was added. After stirring an additional hour at ambient temperature the reaction was quenched with $H_2O$. The reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer was acidified to pH 4 with 1 N HCl. Extraction with $CH_2Cl_2$ (2 x 30 mL) and drying over $MgSO_4$ afforded 0.31 g of crude product. Flash chromatography (silica, 3% MeOH/$CH_2Cl_2$) afforded 0.25 g (83%) of the title compound as an oil.

Anal. for: $C_{31}H_{35}NO_2 \cdot 0.06\ CH_2Cl_2$:

Calc'd: C, 81.31; H, 7.72; N, 3.05.

Found: C, 81.31; H, 7.39; N, 2.86.

C. **3,4-Dihydro-6-(phenylacetyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone**

Jones reagent (1.25 M, 1.8 mL, 2.2 mmol) was added in 0.45 mL portions over 30 minutes to a solution of the title B compound (0.19 g, 0.41 mmol) in acetone (9 mL) stirring at 0°C. Once addition had been completed, the ice bath was removed and the reaction allowed to stir at ambient temperature. After 45 minutes, the reaction was quenched with isopropanol (2.8 mL) and then evaporated *in vacuo*. The residue was transferred to a separatory funnel with $CH_2Cl_2$/2 N NaOH. Extraction with $CH_2Cl_2$ (2 x 60 mL) and drying over $MgSO_4$ afforded 0.14 g of crude product. Flash chromatography (silica, 15 mm dia, 3% MeOH/$CH_2Cl_2$) afforded 0.13 g (73%) of product. Recrystallization from hot EtOH (8 mL) gave pure crystalline title compound.

mp (°C) 129.0-130.5.

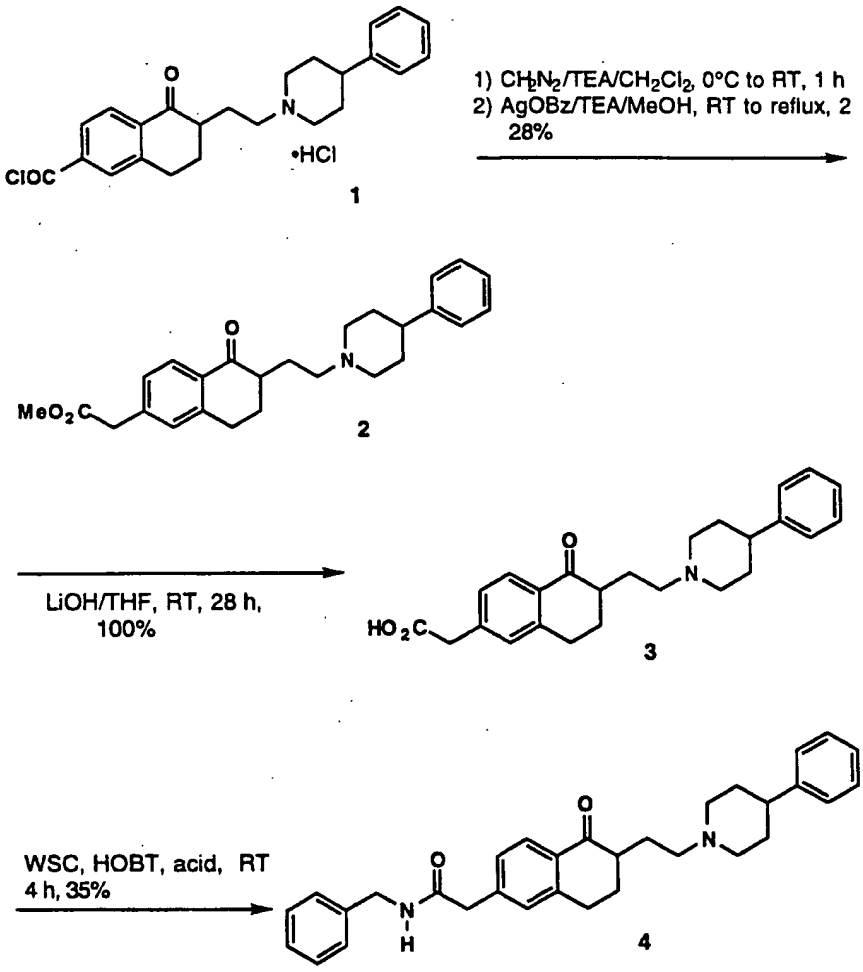
Anal. for: $C_{31}H_{33}NO_2 \cdot 0.32\ H_2O$:

Calc'd: C, 81.41; H, 7. 41; N, 3.06.

Found: C, 81.41; H, 7.14; N, 2.95.

**Example 213**

**5,6,7,8-Tetrahydro-5-oxo-N-(phenylmethyl)-6-[2-(4- phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetamide**




**A. 5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetic acid, methyl ester**

Diazomethane was prepared by adding N-methyl-N-nitrosourea (1.5 g, 15 mmol) to a mixture of 40% KOH (10 mL) and ether (20 mL) stirring at 0°C in an Erlenmeyer flask. Once the bubbling had ceased, THF (10 mL) was added and the organic layer was transferred dropwise with a fire polished Pasteur pipette to a solution of the title compound of Example 145, part A (0.47 g, 0.92 mmol) and triethylamine (0.13 mL, 0.90 mmol) in $CH_2Cl_2$ (10 mL). Additional $CH_2Cl_2$ (~10 mL) was added to maintain solubility. After 1 hour stirring at ambient temperature, the reaction was evaporated *in vacuo*. The residue was dissolved in methanol (20 mL) and AgOBz • TEA (0.1 g in 2.0 mL, 0.28 mL, 0.06 mmol) was added. After stirring at ambient temperature for 1 hour the reaction was refluxed. After 1 hour, the reaction was filtered through Celite to afford 0.68 g of crude product after evaporation of the solvent. Flash chromatography (silica gel, 3% MeOH/$CH_2Cl_2$) afforded 0.10 g (28%) of the title compound as an oil.

Anal. for: $C_{26}H_{31}NO_3 \cdot 1.10\ H_2O$:

Calc'd: C, 73.41; H, 7.87; N, 3.29.

Found: C, 73.41; H, 7.58; N, 3.50.

**B. 5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetic acid**

Lithium hydroxide (1 N in $H_2O$, 0.41 mL, 0.41 mmol) was added to a solution of the title A compound (0.15 g, 0.37 mmol) stirring in THF (3.6 mL). After stirring at ambient temperature for 28 hours, the reaction mixture was evaporated *in vacuo*. The residue was transferred to a separatory funnel with $H_2O$ and the pH adjusted to 7.0 with 1 N NaOH. Extraction with 10% isopropanol/$CH_2Cl_2$ (6 x 50 mL) and drying over $MgSO_4$ afforded 0.14 g (100%) of the title compound after evaporation of the solvent. MS (ESI) 392 (M + H).

**C. 5,6,7,8-Tetrahydro-5-oxo-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetamide**

1-Hydroxybenzotriazole hydrate (HOBT, 50 mg, 0.37 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC, 112 mg, 0.37 mmol) were added to a solution of the title B compound (0.14 g, 0.36 mmol) in $CH_2Cl_2$ (1.6 mL) and DMF (0.40 mL) stirring at ambient temperature. After stirring for 30 minutes, benzylamine (38 mg, 39 mL, 0.36 mmol) in $CH_2Cl_2$ (0.46 mL) was added. After stirring for 4 hours, the reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer adjusted to pH 8.0 with saturated $NaHCO_3$. Extraction with $CH_2Cl_2$ (2 x 30 mL) and drying over $MgSO_4$ afforded 0.70 g of crude product after evaporation of the solvent. Flash chromatography (silica gel, 3% MeOH/$CH_2Cl_2$) afforded 61 mg (35%) of the title compound.

mp (°C) 144.0-146.0.

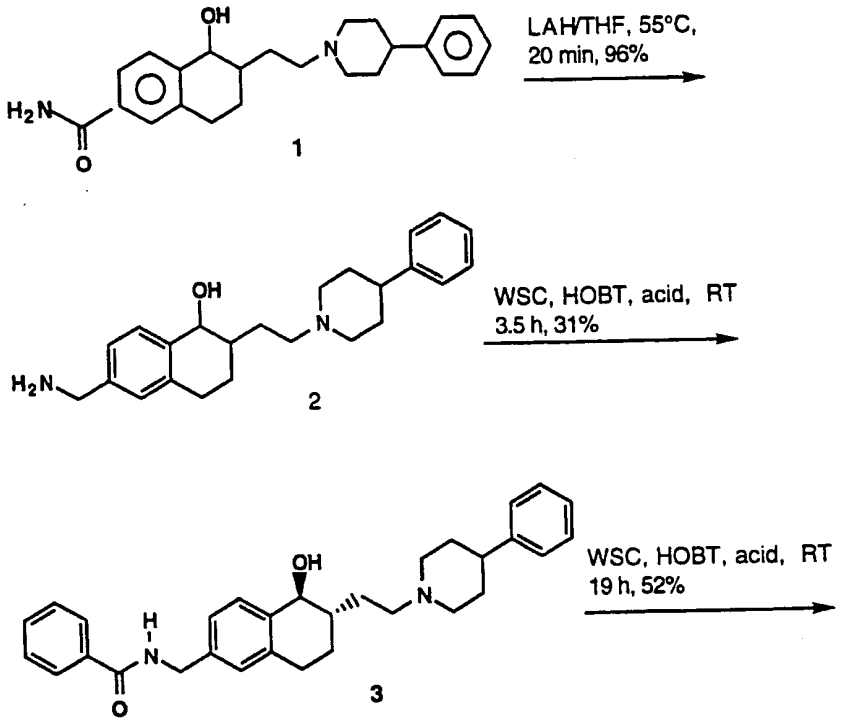
Anal. for: $C_{32}H_{36}N_2O_2 \cdot 0.10\ CH_2Cl_2 \cdot 1.22\ H_2O$:

Calc'd: C, 75.44; H, 7.62; N, 5.48.

Found: C, 75.44; H, 7.24; N, 5.43.

**Example 214**

**N-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzeneacetamide**




**A. 5,6,7,8-Tetrahydro-5-hydroxy-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-(methylamino)naphthalene**

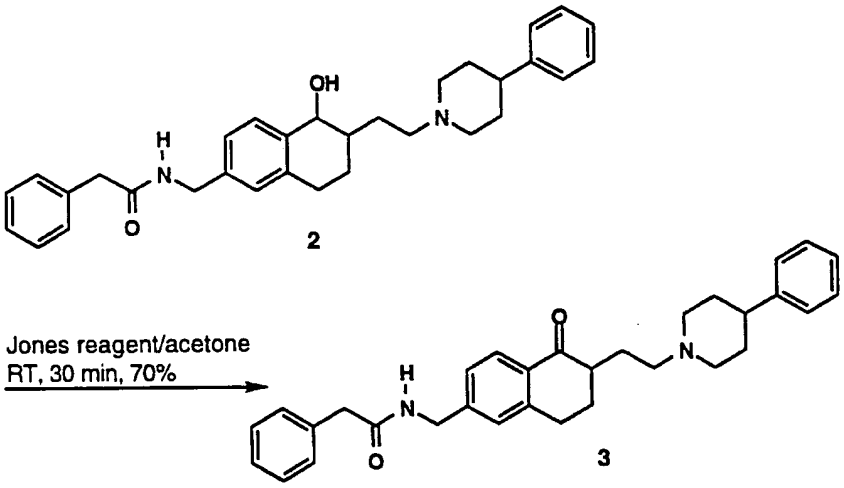
Lithium aluminum hydride (50 mg, 1.3 mmol) and THF (0.6 mL) were stirred under agon in a flame dried flask. The title compound of Example 160 (60 mg, 0.16 mmol in THF (0.3 mL) was then added. After stirring at ambient temperature for 20 minutes and at 50°C for 20 minutes, the reaction was allowed to cool to room temperature and $H_2O$ (2 drops) was added. $Na_2SO_4 \cdot 10\ H_2O$ (15 mg) was added and then water was added dropwise to the reaction mixture as it stirred vigorously until the precipitate became granular. Filtration rinsing with THF afforded 56 mg of the title compound.

**B. trans-N-[[5,6,7,8-Tetrahydro-5-hydroxy-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzamide**

1-Hydroxybenzotriazole hydrate (22 mg, 0.16 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC, 49 mg, 0.16 mmol) were added to a solution of benzoic acid (18 mg, 0.15 mmol) in $CH_2Cl_2$ (0.70 mL) and DMF (0.18 mL) stirring at ambient temperature. After stirring for 30 minutes, the title A compound (56 mg, 0.15 mmol) in $CH_2Cl_2$ (0.20 mL) was added. After stirring for 3.5 hours, the reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer adjusted to pH 8.0 with saturated $NaHCO_3$. Extraction with $CH_2Cl_2$ (2 x 20 mL) and drying over $MgSO_4$ afforded 80 mg of crude product after evaporation of the solvent. Flash chromatography (silica, 11 mm dia, 4% MeOH/$CH_2Cl_2$) afforded 22 mg (31%) of the title compound. mp (°C) 69.0-72.0.

**Example 214a**

**3,3-Dimethyl-N-[[5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]butanamide**
**and**
**N-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzeneacetamide**




**A. N-[[5,6,7,8-Tetrahydro-5-hydroxy-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]-benzeneacetamide**

1-Hydroxybenzotriazole hydrate (HOBT, 39 mg, 0.29 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC, 87 mg, 0.29 mmol) were added to a solution of phenylacetic acid (36 mg, 0.28 mmol) in $CH_2Cl_2$ (1.3 mL) and DMF (0.32 mL) stirring at ambient temperature. After stirring for 30 minutes, the title A compound of Example 214 (100 mg, 0.27 mmol) in $CH_2Cl_2$ (0.36 mL) was added. After stirring for 19 hours, the reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer adjusted to pH 8.0 with saturated $NaHCO_3$. Extraction with $CH_2Cl_2$ (2 x 20 mL) and drying over $MgSO_4$ afforded 150 mg of crude product after evaporation of the solvent. Flash chromatography (silica gel, 3% MeOH/$CH_2Cl_2$) afforded 68 mg (52%) of the title compound.

**B. N-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzene-acetamide**

Jones reagent (1.25 M, 0.57 mL, 0.71 mmol) was added in 0.14 mL portions over 30 minutes to a solution of the title A compound (65 mg,

0.13 mmol) in acetone (2.8 mL) stirring at 0°C. Once addition had been completed the ice bath was removed and the reaction allowed to stir at ambient temperature. After 30 minutes, the reaction was quenched with isopropanol (0.9 mL) and then evaporated *in vacuo*. The residue was transferred to a separatory funnel with $CH_2Cl_2$/0.1 N NaOH. Extraction with $CH_2Cl_2$ (2 x 25 mL) and drying over $MgSO_4$ afforded 59 mg of crude product. Flash chromatography (silica gel, 11 mm dia, 3% MeOH/$CH_2Cl_2$) afforded 44 mg (70%) of the title compound as an oil.

Anal. for: $C_{32}H_{36}N_2O_2 \cdot 0.52\ H_2O$:

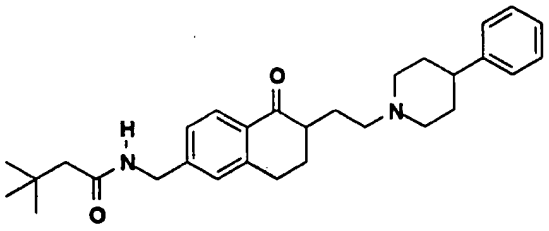
Calc'd: C, 78.43; H, 7.62; N, 5.72.

Found: C, 78.43; H, 7.45; N, 5.75.

**Using methodology analogous to that described for the title compound of Example 214, the compound of Example 214a was prepared:**

**Example 214b**

**3,3-Dimethyl-N-[[5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]butanamide**



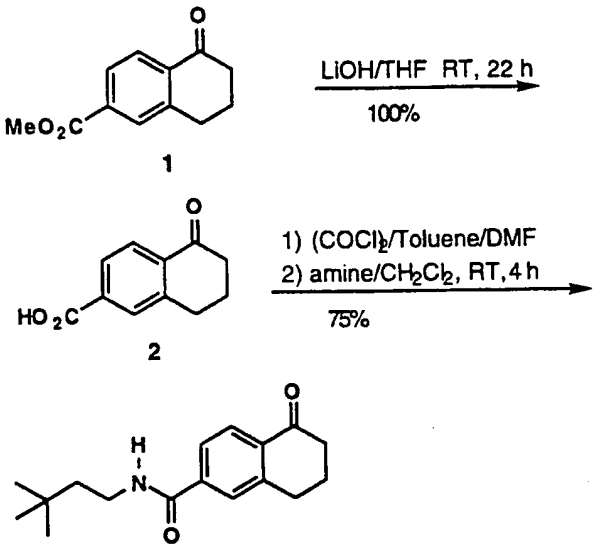

Anal. for: $C_{30}H_{40}N_2O_2 \cdot 0.90\ H_2O$:

Calc'd: C, 75.56; H, 8.84; N, 5.87.

Found: C, 75.56; H, 8.77; N, 5.83.

## Example 215

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalene-carboxamide**




BMS-205594

**A. 5,6,7,8-Tetrahydro-5-oxo-2-naphthalenecarboxylic acid**

Lithium hydroxide (1 M in $H_2O$, 5.3 mL, 5.3 mmol) was added to a solution of compound 1 (1.0 g, 4.9 mmol) in THF (48 mL) which had been sparged with argon for 15 minutes. After stirring at ambient temperature under argon for 22 hours, the reaction was evaporated *in vacuo* . The residue was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer was acidified to pH 4 with 1N HCl. Extraction with 10% isopropanol/$CH_2Cl_2$ (3 x 35 mL) and drying over $MgSO_4$ afforded 0.94 g (100%) of the title compound.

**B. N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarbox amide**

Oxalyl chloride (2M in $CH_2Cl_2$, 4.3 mL, 8.6 mmol) was added to a stirring suspension of acid **2** (0.90 g, 4.3 mmol) in toluene (20 mL). DMF (1 drop) was added and the reaction began bubbling. After 2 hours, the reaction was evaporated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (21 mL) and 3,3-dimethylbutylamine (0.87 g, 1.2 mL, 8.6 mmol) was added. After stirring at ambient temperature for 4 hours, the reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$. Extraction with $CH_2Cl_2$ (3 x 30 mL) and drying over $MgSO_4$ afforded 1.4 g of product after evaporation of the solvent. Flash chromatography (silica gel, 37 mm dia, 40% EtOAc/hexane) afforded 1.2 g of product. Recrystallization from EtOAc/hexane (10 mL/10 mL) afforded 0.89 g (75%) of pure crystalline title compound.

mp (°C) 133.0-134.5.

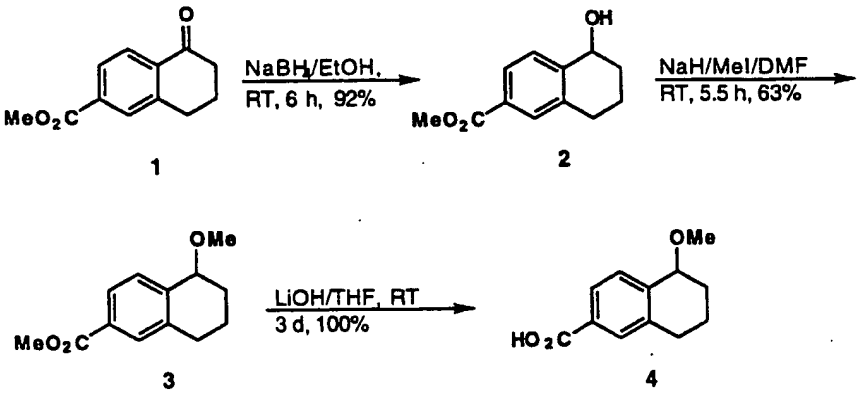
Anal. for: $C_{17}H_{23}NO_2$:

Calc'd: C, 74.69; H, 8.48; N, 5.12.

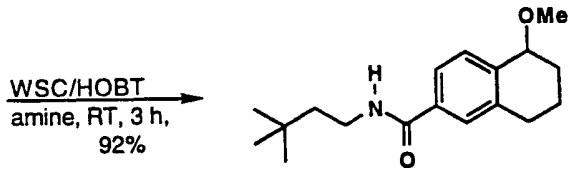
Found: C, 74.77; H, 8.42; N, 4.99.

**Example 216**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-methoxy-2-naphthalenecarboxamide**




1 2 3 4




5

**A. 5,6,7,8-Tetrahydro-5-hydroxy-2-naphthalenecarboxylic acid, methyl ester**

Sodium borohydride (37 mg, 1.0 mmol) was added to a stirring solution of 1 (For the preparation of 1, see Example 216 0.20 g, 1.0 mmol) in ethanol (11 mL). After stirring at ambient temperature for 5 hours, the reaction was quenched with $H_2O$ and transferred to a separatory funnel with $CH_2Cl_2/H_2O$. The reaction was acidified to pH 4 with 1N HCl and then basified to pH 7.5 with saturated $NaHCO_3$. Extraction with $CH_2Cl_2$ (2 x 20 mL) and drying over $MgSO_4$ afforded 0.20 g of the title compound. $R_f$ (silica, 25% EtOAc/hexane) = 0.15.

**B. 5,6,7,8-Tetrahydro-5-methoxy-2-naphthalene-carboxylic acid, methyl ester**

Sodium hydride (80% oil dispersion, 28 mg, 0.93 mmol) was added to a solution of 2 (0.19 g, 0.93 mmol) in DMF (2 mL) stirring at 0°C. Methyl iodide (0.13 g, 58 mL, 0.93 mmol) was added. After stirring at 0°C for 2 hours and at ambient temperature for 30 minutes, additional sodium hydride (14 mg, 0.47 mmol) and methyl iodide (29 mL, 0.47 mmol) were added. After stirring an additional 3 hours, the reaction was quenched with 0.1N HCl and transferred to a separatory funnel with $CH_2Cl_2$. Extraction with $CH_2Cl_2$ (2 x 40 mL) and drying over $MgSO_4$ afforded 0.33 g of crude product after evaporation of the solvent. Flash chromatography (silica, 25 mm dia, 10% EtOAc/hexane) afforded 0.13 g (63%) of the title compound.

**C. 5,6,7,8-Tetrahydro-5-methoxy-2-naphthalene-carboxylic acid**

Lithium hydroxide (1.0 M in $H_2O$, 2.7 mL, 2.7 mmol) was added to a solution of the title B compound (0.55 g, 2.5 mmol) in THF (24 mL). After stirring at ambient temperature for 3 days, the reaction was evaporated *in vacuo* and the residue transferred to a separatory funnel with $CH_2Cl_2/H_2O$. The first extraction with $CH_2Cl_2$ (40 mL) was discarded and then the aqueous layer was acidified with 1 N HCl. Extraction with $CH_2Cl_2$ (2 x 50 mL) and drying over $MgSO_4$ afforded 0.52 g (100%) of the title compound.

**D. N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-methoxy-2-naphthalenecarboxamide**

1-hydroxybenzotriazole hydrate (HOBT, 0.17 g, 1.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC, 0.37 g, 1.2 mmol) were added to a solution of the title C compound (0.27 g, 1.1 mmol) in $CH_2Cl_2$ (5.3 mL) and DMF (1.4 mL) stirring at ambient temperature. After stirring for 30 minutes, 3,3-dimethylbutylamine (0.15 g, 0.20 mL, 1.5 mmol) in $CH_2Cl_2$ (0.60 mL) was added. After stirring for 3 hours, the reaction was transferred to a separatory funnel with $CH_2Cl_2/H_2O$ and the aqueous layer adjusted to pH 2.0 with 1 N HCl. Extraction with $CH_2Cl_2$ (2 x 30 mL), washing the combined organic layers with saturated $NaHCO_3$, and drying over $MgSO_4$ afforded 0.37 g of crude product after evaporation of the solvent. Flash chromatography (silica, 25 mm dia, 30% EtOAc/hexane) afforded 0.30 g (92%) of the title compound. mp (°C) 72.0-73.0.

Anal. for: $C_{18}H_{27}NO_2$:

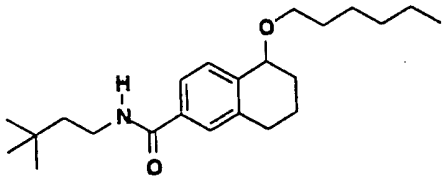
Calc'd: C, 74.70; H, 9.40; N, 4.84.

Found: C, 74.46; H, 9.36; N, 4.80.

**Using methodology analogous to that described for the title compound of Example 216, the compound of Example 217 was prepared:**

**Example 217**

**N-(3,3-Dimethylbutyl)-5-(hexyloxy)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide**



For BMS-206115: $R_f$ (silica, 25% EtOAc/hexane) = 0.25.

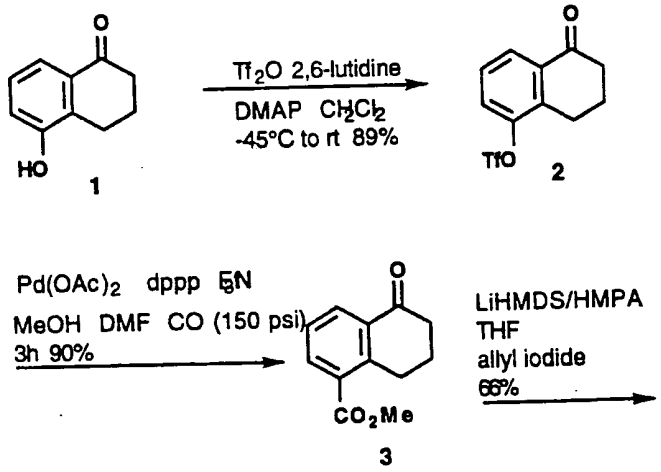
Anal. for: $C_{23}H_{37}NO_2 \cdot 0.22\ H_2O$:

Calc'd: C, 76.01; H, 10.38; N, 3.85.

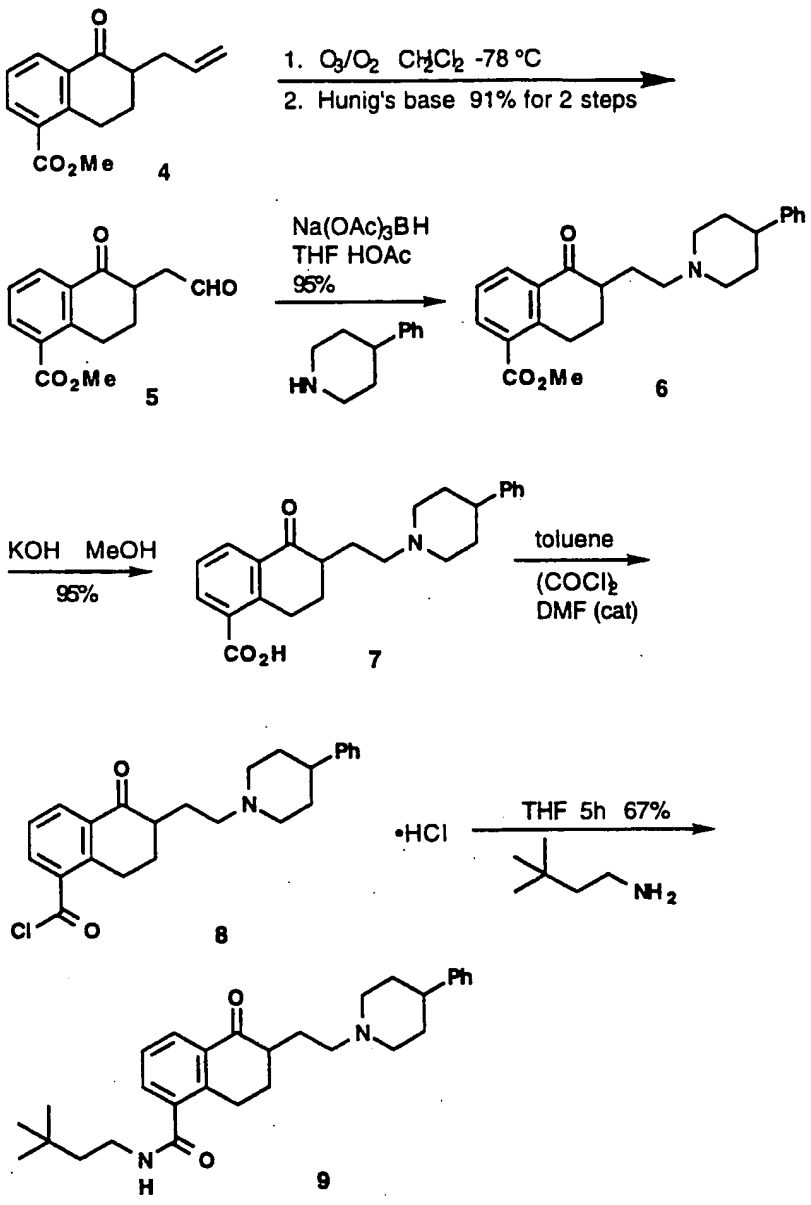
Found: C, 76.01; H, 10.24; N, 3.85.

**Example 218**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide**




1 2 3




5

**A. Compound 2**

10 To a -45°C suspension of 5-hydroxy-1-tetralone (30.0 g, 0.185 mol), 4-(dimethylamino)pyridine (4.5 g, 37 mmol) and 2,6-lutidine (25.9 mL, 0.222 mol) in methylene chloride (1.8 L) was added, dropwise, triflic anhydride (37.3 mL, 0.222 mol) over a 30-minute period. The reaction was allowed to come to room temperature and stirred for 1 hour. The

reaction was washed with water (500 mL), 1 N HCl (600 mL), water (500 mL), saturated $NaHCO_3$ (400 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide 48.4 g (89%) of an oil.

**B. Methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-1-carboxylate**

A 450-mL Parr bomb was charged with methanol (81 mL), DMF (160 mL), compound 2 (24.0 g, 81.6 mmol), palladium acetate (549 mg, 2.45 mmol), 1,3-bis(diphenylphosphino)-propane (1.01 g, 2.45 mmol), and triethylamine (23 mL, 163 mmol). The bomb was purged with carbon monoxide using 2 fill/vent cycles. The bomb was repressurized to 150 psi and was heated to 80°C for 3 hours. During this time additional CO was admitted to maintain the pressure at 150 psi. The bomb was cooled to room temperature and vented. A second identical run was made. The combined reactions were diluted with methylene chloride (2 L), washed with water (4 x 800 mL), dried ($MgSO_4$) and concentrated *in vacuo* to a black solid. Chromatography (flash, silica, 120 mm dia x 20 cm, 2% ethyl acetate/methylene chloride) provided semi-pure product. Recrystallization of this material from hot hexanes in 2 crops followed by chromatography of the final mothor liquors (silica gel, methylene chloride (700 mL) then 2% ethyl acetate/methylene chloride) provided a total of 30.3 g (90%) of the title compound.

**C. Methyl 5-oxo-6-(2-propenyl)-5,6,7,8-tetrahydro-naphthalene-1-carboxylate**

To a -78°C suspension of the title B compound (30.3 g, 143 mmol) in dry THF (150 mL) was added, dropwise over a 30-minute period, lithium hexamethyldisilazide (1 M in THF, 134 mL, 134 mmol). The reaction was stirred for 10 minutes and then HMPA (28 mL, 160 mmol) was added, dropwise, over 2 minutes. The reaction was allowed to come to room temperature whereupon allyl iodide (74.6 mL, 444 mmol) was added all at once. The internal temperature rose to 40°C and then fell to room temperature over a 1 hour period. After an additional 30 minutes,

the reaction was diluted with ether (2.5 L), washed with 0.5 N HCl (500 mL), water (500 mL), saturated $NaHCO_3$ (250 mL), saturated sodium chloride (500 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (silica gel, 50% methylene chloride/hexanes) in 2 portions followed by rechromatography of impure fractions provided 23.1 g (66%) of the title compound.

**D. Compound 5**

Using a Welsbach ozonizer, $O_3/O_2$ was bubbled into a -78°C solution of the title C compound (5.26 g, 21.5 mmol) in methylene chloride (200 mL) until a blue color persisted. The reaction was sparged with nitrogen to discharge the excess ozone and diisopropylethylamine (7.5 mL, 43 mmol) was then added dropwise. The reaction was allowed to come to room temperature and stirred for 1.5 hours. The reaction was then washed with 0.3 N HCl (200 mL), water (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (silica gel, 25% ethyl acetate/hexanes:methylene chloride 9:1) provided 4.81 g (91%) of the desired aldehyde which was used directly in the next reaction.

**E. Methyl 5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxylate**

To a solution of the title D compound (4.81 g, 19.5 mmol) in THF (200 mL) was added, sequentially, 4-phenylpiperidine (4.09 g, 25.4 mmol), acetic acid (1.1 mL, 19.5 mmol), and sodium triacetoxyborohydride (6.62 g, 31.3 mmol). The reaction was stirred for 4 hours and diluted with methylene chloride (1.5 L). The mixture was washed with 0.5 N sodium carbonate (2 x 200 mL), saturated sodium chloride (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (silica gel, 50% ethyl acetate/hexanes then ethyl acetate) provided the title compound (7.25 g, 95%).

**F. 5,6,7,8-Tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxylic acid**

To a solution of the title E compound (7.00 g, 17.9 mmol) in methanol/methylene chloride (100 mL/10 mL) was added, dropwise, 2 N KOH (25 mL). A transient second phase formed. After 17 hours, an additional 10-mL portion of KOH was added. After 2 hours, the reaction was adjusted to pH 8 with hydrochloric acid and the organics were removed *in vacuo*. The residue was mixed with water (150 mL) and the pH was readjusted to 8. The solid was collected by filtration, washed with water (3 x 10 mL) and dried (finally over $P_2O_5$) to provide 6.43 g (95%) of a white solid.

**G. 5,6,7,8-Tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarbonyl chloride hydrochloride**

To a suspension of the title F compound (6.4 g, 17 mmol) in toluene (150 mL) was added 1 drop of DMF and then, dropwise, oxalyl chloride (3.0 mL, 34 mmol). After 6 hours, the reaction was concentrated *in vacuo* to a yellow solid (7.23 g, 98%).

**H. N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide**

To a partial solution of the title G compound (240 mg, 0.555 mmol) in THF (3 mL) was added 3,3-dimethylbutylamine (0.16 mL, 1.2 mmol). After stirring for 5 hours, the reaction was diluted with methylene chloride (20 mL). The mixture was washed with 0.2 N NaOH (10 mL) causing a thick emulsion to form. The mixture was shaken with saturated sodium chloride (3 x 20 mL) which allowed separation of the organic layer. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization of the product from ethanol/water (ca. 8 mL, ca. 2/1) provided shiny white plates (172 mg, 67%): mp (°C) 157.5-158.0.

Anal. for: $C_{30}H_{40}N_2O_2$:

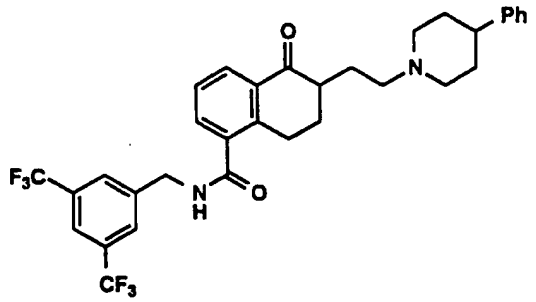
Calc'd: C, 78.22; H, 8.75; N, 6.08.

Found: C, 78.20; H, 8.88; N, 5.98.

**Using methodology analogous to that described for the title compound of Example 218, the compounds of Examples 219 to 236 were prepared:**

**Example 219**

**N-[[3,5 Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalene-carboxamide**




mp (°C) 171.5-173.0.

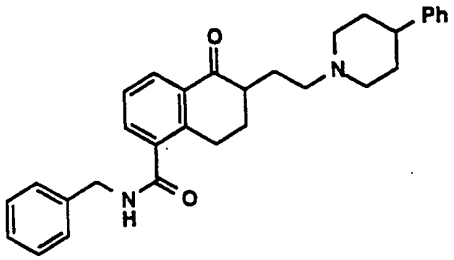
Anal. for: $C_{33}H_{32}F_6N_2O_2$:

Calc'd: C, 67.55; H, 5.35; N, 4.65; F, 18.92.

Found: C, 65.57; H, 5.15; N, 4.62; F, 18.88.

**Example 220**

**5,6,7,8-Tetrahydro-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide**



mp (°C) 175.0-176.0.

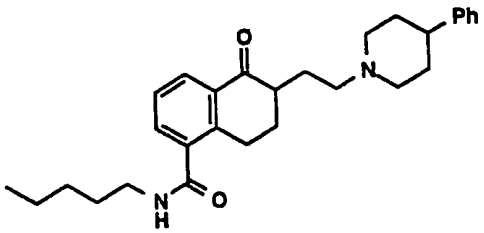
Anal. for: $C_{31}H_{34}ClN_2O_2$:

Calc'd: C, 79.80; H, 7.34; N, 6.00.

Found: C, 79.83; H, 7.32; N, 5.95.

**Example 221**

**5,6,7,8-Tetrahydro-5-oxo-N-pentyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 129.0-130.0.

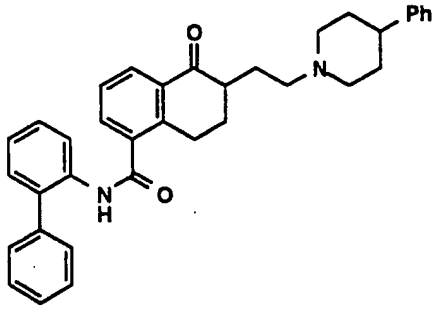
Anal. for: $C_{29}H_{38}N_2O_2$:

Calc'd: C, 77.99; H, 8.58; N, 6.27.

Found: C, 78.02; H, 8.61; N, 6.28.

**Example 222**

**N-([1,1'-Biphenyl]-2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 144.0-145.0.

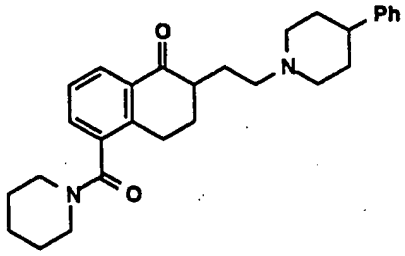
Anal. for: $C_{36}H_{36}N_2O_2$:

Calc'd: C, 81.79; H, 6.86; N, 5.30.

Found: C, 81.58; H, 6.74; N, 5.20.

**Example 223**

**1-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenyl]carbonyl]piperidine, (E)-2-butenedioate (1:1)**



mp (°C) 118.

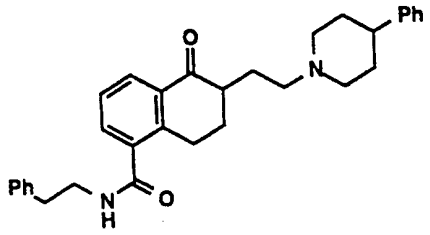
Anal. for: $C_{29}H_{36}N_2O_2 \bullet 1.0\ C_4H_4O_4 \bullet 0.83\ H_2O$:

Calc'd: C, 68.75; H, 7.25; N, 4.63.

Found: C, 68.98; H, 7.29; N, 4.68.

**Example 224**

**5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 143.5-144.5.

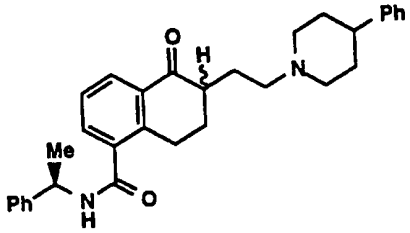
Anal. for: $C_{32}H_{36}N_2O_2$:

Calc'd: C, 79.97; H, 7.55; N, 5.83.

Found: C, 79.99; H, 7.41; N, 5.74.

**Example 225**

**5,6,7,8-Tetrahydro-5-oxo-N-[(R)-1-phenylethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 169.5-170.0.

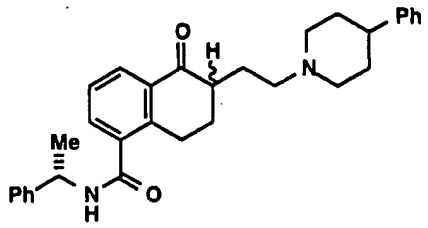
Anal. for: $C_{32}H_{36}N_2O_2$:

Calc'd: C, 79.97; H, 7.55; N, 5.83.

Found: C, 79.86; H, 7.48; N, 5.76.

**Example 226**

**5,6,7,8-Tetrahydro-5-oxo-N-[(S)-1-phenylethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 169.5-170.5.

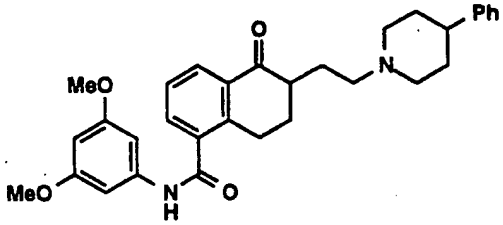
Anal. for: $C_{32}H_{36}N_2O_2$:

Calc'd: C, 79.97; H, 7.55; N, 5.83.

Found: C, 79.78; H, 7.52; N, 5.81.

**Example 227**

**N-(3,5-Dimethoxyphenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 141.0-144.5.

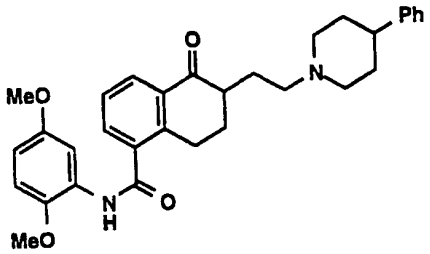
Anal. for: $C_{32}H_{36}N_2O_4$:

Calc'd: C, 74.97; H, 7.08; N, 5.46.

Found: C, 74.78; H, 6.90; N, 5.35.

**Example 228**

**N-(2,5-Dimethoxyphenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**




mp (°C) 117.0-118.5.

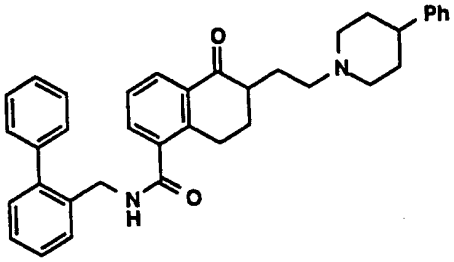
Anal. for: $C_{32}H_{36}N_2O_4$:

Calc'd: C, 74.97; H, 7.08; N, 5.46.

Found: C, 75.01; H, 6.98; N, 5.41.

**Example 229**

**N-([1,1'-Biphenyl]-2-ylmethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**




mp (°C) 157.0-158.5.

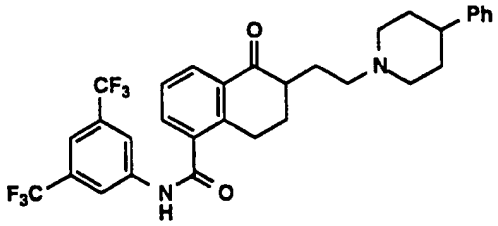
Anal. for: $C_{37}H_{38}N_2O_2 \cdot 0.29\ H_2O$:

Calc'd: C, 81.10; H, 7.10; N, 5.11.

Found: C, 81.09; H, 6.82; N, 5.11.

**Example 230**

**N-(3,5-Bis(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 178-181.

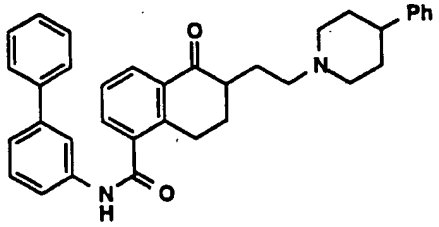
Anal. for: $C_{32}H_{30}F_6N_2O_2$:

Calc'd: C, 65.30; H, 5.14; F, 4.76; N, 19.37.

Found: C, 65.18; H, 5.07; F, 4.46; N, 19.08.

**Example 231**

**N-([1,1'-Biphenyl]-3-yl))-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



mp (°C) 222-224.

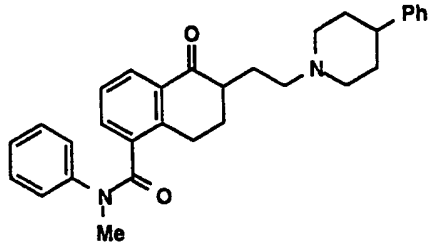
Anal. for: $C_{36}H_{36}N_2O_2$:

Calc'd: C, 81.79; H, 6.86; N, 5.30.

Found: C, 81.51; H, 6.64; N, 5.15.

**Example 232**

**5,6,7,8-Tetrahydro-N-methyl-5-oxo-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**




mp (°C) 139.0-140.0.

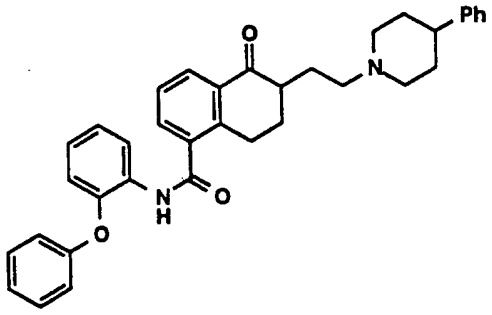
Anal. for: $C_{31}H_{34}N_2O_2 \cdot 0.20\ H_2O$:

Calc'd: C, 79.20; H, 7.37; N, 5.96.

Found: C, 79.21; H, 7.27; N, 5.79.

**Example 233**

**5,6,7,8-Tetrahydro-5-oxo-N-(2-phenoxyphenyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**



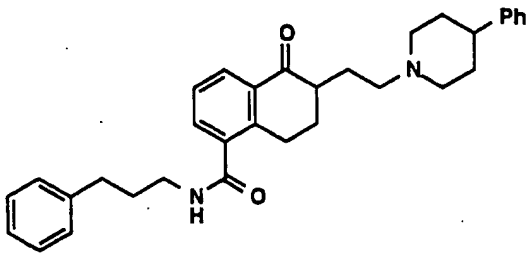

Anal. for: $C_{36}H_{36}N_2O_3$:

Calc'd: C, 79.38; H, 6.66; N, 5.14.

Found: C, 79.41; H, 6.43; N, 5.04.

**Example 234**

**5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(3-phenylpropyl)-1-naphthalenecarboxamide**




mp (°C) 158.6-160.0.

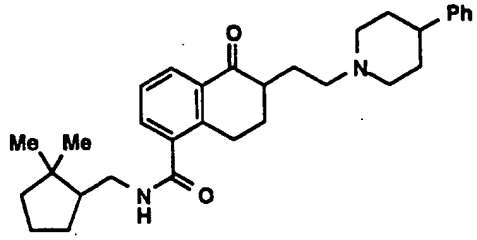
Anal. for: $C_{33}H_{38}N_2O_2$:

Calc'd: C, 80.13; H, 7.74; N, 5.66.

Found: C, 80.20; H, 7.81; N, 5.60.

**Example 235**

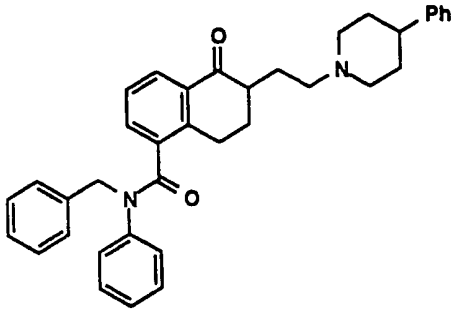
**N-[(2,2-Dimethylcyclopentyl)methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide**




mp (°C) 110.0-112.0.

**Example 236**

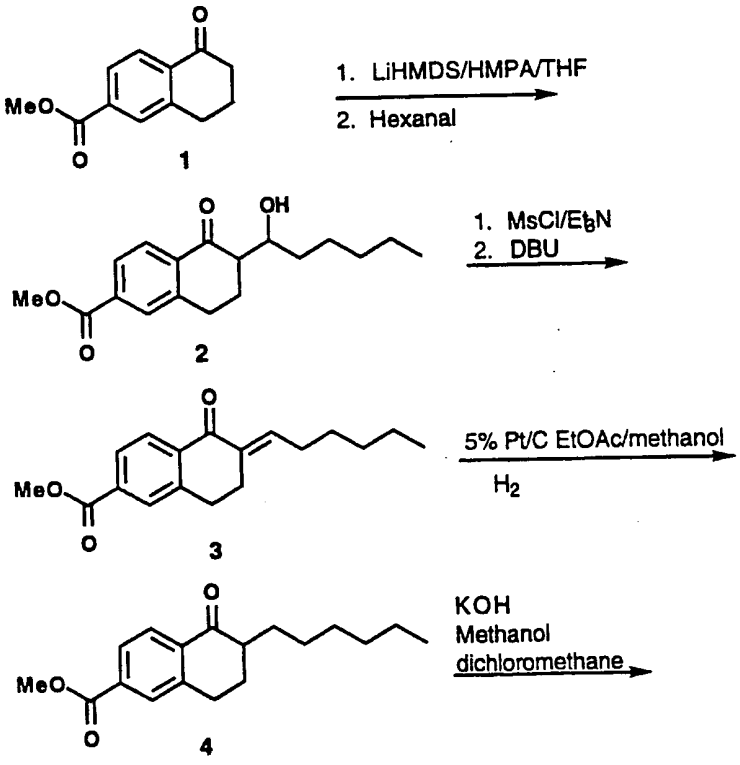
**5,6,7,8-Tetrahydro-N-phenyl-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide**

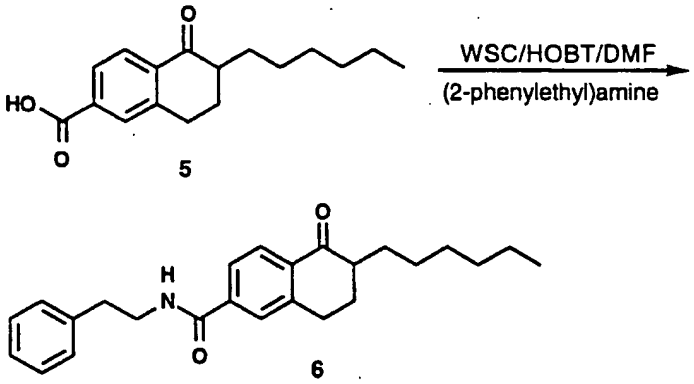



Molecular Weight (Esi): 543.

**Example 237**

**6-Hexyl-5,6,7,8-tetrahydro-5-oxo-N-(2-phenylethyl)-2-naphthalenecarboxamide**






**A. Methyl 6-((1-hydroxy)hexyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxylate**

A slurry of methyl 5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxylate (500 mg, 2.45 mmol) in THF was placed in a -78°C bath and lithium hexamethylsilazide (1.0 M in THF, 2.7 mL) and then HMPA (0.51 mL, 2.9 mmol) were added dropwise. After 20 minutes, hexanal (0.31 mL, 2.6 mmol) was added dropwise. After stirring for 4 hours, the reaction was partitioned between 0.3 N HCl (25 mL) and ether (100 mL). The organic layer was washed with water (25 mL), saturated sodium bicarbonate (25 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography (silica gel, 25% ethyl acetate/hexanes) provided 635 mg (85%) of a pale yellow oil.

**B. Methyl 6-(hexylidine)-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxylate**

To a 0°C solution of the title A compound (613 mg, 2.01 mmol) in dichloromethane (10 mL) was added triethylamine (0.84 mL, 6.0 mmol) and then, dropwise, mesyl chloride (0.34 mL, 4.4 mmol). An additional 0.84mL portion of triethylamine was added followed by dropwise additionof a 0.34 mL portion of mesylchloride. After 1h, DBU (0.75 mL, 5.0 mmol) was added dropwise. After an additional 1h, DBU (0.7 mL) was added. After 30 min., the reaction was diluted with ether (75 mL) washed with 1 N HCl (2 x 25 mL), water (25 mL), saturated sodium

bicarbonate (2 x 25 mL), dried (magnesium sulfate) and concentrated *in vacuo* to provide a yellow solid. Flash chromatography (silica gel, 10% ethyl acetate/hexanes) provided a pale yellow solid.

C. **Methyl 6-(hexyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxylate.**

To a solution of the title B compound in methanol/ethyl acetate (6 mL/4 mL) was added 5% Pt/C (30 mg). The reaction was stirred under a hydrogen balloon for 2 hours. The reaction was filtered through Celite and the pad was rinsed with ethyl acetate/methanol 1/1 (3 x 5 mL). The combined filtrates were concentrated *in vacuo*. Flash chromatography (silica gel, 10% ethyl acetate/hexanes then 20% ethyl acetate/hexanes) provided a pale yellow oil (424 mg, 73%).

D. **6-(Hexyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxylic acid**

To a solution of the title C compound (402 mg, 1.39 mmol) in methanol (12 mL) and dichloromethane (1 mL) was added 2 N KOH (3 mL). The reaction was stirred for 2 hours and the pH was adjusted to 2. The reaction was concentrated to remove the organic solvents. The residue was diluted with water (20 mL) and the solid was collected by filtration, washed with water (4 x 10 mL) and dried *in vacuo* to provide 339 mg (89%) of a white solid.

E. **6-Hexyl-5,6,7,8-tetrahydro-5-oxo-N-(2-phenylethyl)-2-naphthalenecarboxamide**

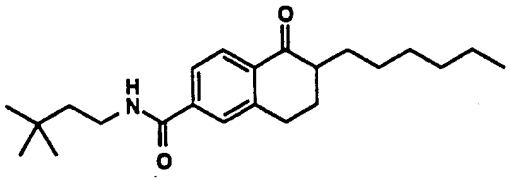
To a solution of the title D compound (100 mg, 0.364 mmol) in DMF (4 mL) were added HOBT (hydrate, 59 mg) triethylamine 0.020 mL, 0.15 mmol) and (2-phenylethyl)amine (0.60 mL, 0.47 mmol). After stirring for 2 hours, the reaction was diluted with ether (25 mL) and was washed with 0.3 N HCl (10 mL), water (10 mL), saturated sodium bicarbonate (10 mL), dried (magnesium sulfate) and concentrated *in vacuo*. Flash

chromatography (silica gel, 25% ethyl acetate/hexanes) provided 134 mg (98%) of a white solid: mp (°C) 125.0-128.0; MS (ESI) m/z 378.

**Using methodology analogous to that described for the title compound of Example 237, the compounds of Examples 238 to 240 were prepared:**

**Example 238**

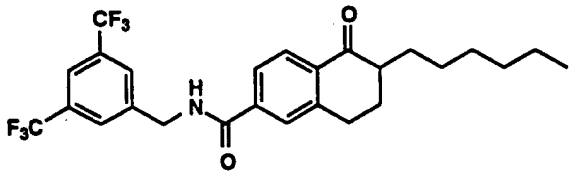
**N-(3,3-Dimethylbutyl)-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide**



mp (°C) 78.0-79.5.
MS (ESI) 358.

**Example 239**

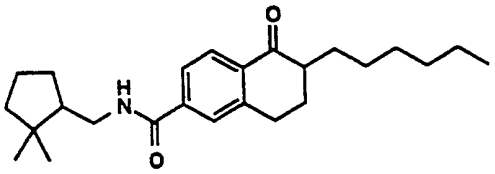
**N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide**



mp (°C) 108.5-110.0.
MS (ESI) 500.

**Example 240**

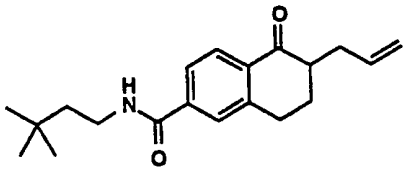
**N-[[2,2-Dimethylcyclopentyl)methyl]-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide**



MS (ESI) 384.

**Example 241**

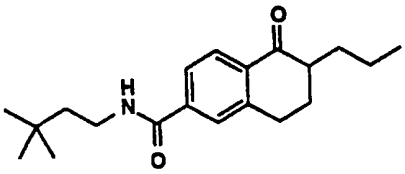
**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-2-naphthalenecarboxamide**



MS (ESI) 314.

**Example 242**

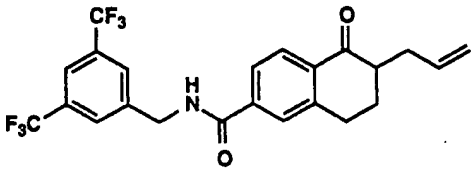
**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-propyl-2-naphthalenecarboxamide**



mp (°C) 111.5-113.5.
MS (ESI) 316.

**Example 243**

**N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-2-naphthalenecarboxamide**

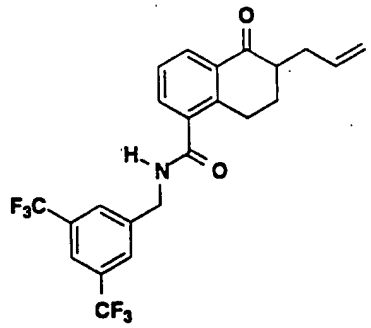


mp (°C) 113.0-114.0.

MS (ESI) 454.

**Example 244**

**N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-1-naphthalenecarboxamide**



mp (°C) 158.0-159.0.

MS (ESI) 454.

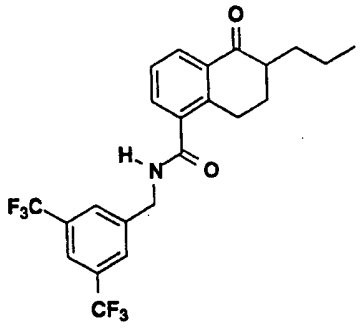
Anal. for: $C_{23}H_{19}F_6NO_2 \bullet 0.04\ H_2O \bullet 0.05\ C_6H_{14}$:

Calc'd: C, 60.77; H, 4.33; N, 3.04; F, 24.75.

Found: C, 60.77; H, 3.98; N, 3.02; F, 24.43.

**Example 245**

**N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-propyl-1-naphthalenecarboxamide**



mp (°C) 171.5-172.5.

MS (ESI) 456.

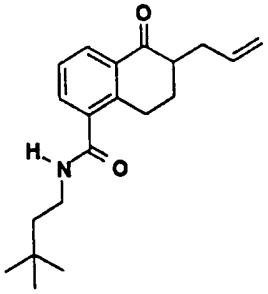
Anal. for: $C_{23}H_{21}F_6NO_2$:

Calc'd: C, 60.39; H, 4.63; N, 3.06; F, 24.92.

Found: C, 60.50; H, 4.56; N, 3.00; F, 24.73.

**Example 246**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-1-naphthalenecarboxamide**



mp (°C) 100.0-102.0.

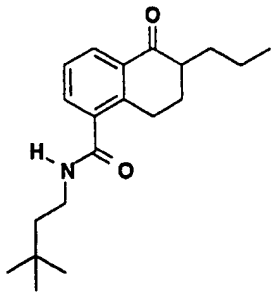
Anal. for: $C_{20}H_{27}NO_2$:

Calc'd: C, 76.64; H, 8.68; N, 4.47.

Found: C, 76.59; H, 8.70; N, 4.43.

**Example 247**

**N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-hydroxy-2-naphthalenecarboxamide**



mp (°C) 127.0-128.0.

Anal. for: $C_{20}H_{29}NO_2$:

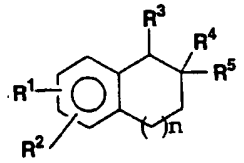
Calc'd: C, 76.15; H, 9.27; N, 4.44.

Found: C, 76.12; H, 9.22; N, 4.39.

**What is Claimed is:**

1. A method of treating cardiac arrhythmia which comprises administering to a mammal in need thereof an effective amount of a compound of the formula

I



where

$R^1$ is halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, (aryl)alkenyl, (aryl)alkynyl, alkoxy, O-alkenyl, O-aryl, O-alkyl(heterocyclo), COO-alkyl,alkanoyl, CO-amino, CO-substituted amino, alkyl-CO-amino, alkyl-CO-substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-alkyl(heterocyclo), N(alkyl)CO-alkyl, N(alkyl)CO-aryl, N(alkyl)CO-heterocyclo, N(alkyl)CO-alkyl(heterocyclo);

$R^2$ is hydrogen, alkyl, halo, aryl, alkoxy, amino, substituted amino;

$R^3$ is oxo, hydroxy, alkoxy, O-COalkyl, -O-COaryl, -O-COheterocyclo, NOH, NO-alkyl, N-amino, N-substituted amino, N-NHCONHalkyl, N-$NHSO_2$alkyl, N-$NHSO_2$aryl, amino, substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-heterocyclo, spiroheterocyclo;

$R^4$ is hydrogen, alkyl, alkyl(COalkyl), alkyl(COOalkyl); or

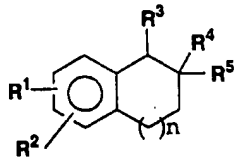
$R^3$ and $R^4$ taken together with the atoms to which they are attached form a five- to seven-membered ring which can contain up to three heteroatoms selected from oxygen, nitrogen and sulfur;

$R^5$ is hydrogen, alkyl, alkenyl, alkyl(heterocyclo), alkyl-NHCO(alkyl), alkyl-NHCO(aryl), alkyl-NHCO(heterocyclo), alkyl-NHCO(alkylheterocyclo); and

n is an integer of 0 to 2.

2. A compound of formula

I




where

$R^1$ is halo, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, (aryl)alkenyl, (aryl)alkynyl, alkoxy, O-alkenyl, O-aryl, O-alkyl(heterocyclo), COO-alkyl,alkanoyl, CO-amino, CO-substituted amino, alkyl-CO-amino, alkyl-CO-substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-alkyl(heterocyclo), N(alkyl)CO-alkyl, N(alkyl)CO-aryl, N(alkyl)CO-heterocyclo, N(alkyl)CO-alkyl(heterocyclo);

$R^2$ is hydrogen, alkyl, halo, aryl, alkoxy, amino, substituted amino;

$R^3$ is oxo, hydroxy, alkoxy, O-COalkyl, -O-COaryl, -O-COheterocyclo, NOH, NO-alkyl, N-amino, N-substituted amino, N-NHCONHalkyl, N-$NHSO_2$alkyl, N-$NHSO_2$aryl, amino, substituted amino, NHCO-alkyl, NHCO-aryl, NHCO-heterocyclo, spiroheterocyclo;

$R^4$ is hydrogen, alkyl, alkyl(COalkyl), alkyl(COOalkyl); or

$R^3$ and $R^4$ taken together with the atoms to which they are attached form a five- to seven-membered ring which can contain up to three heteroatoms selected from oxygen, nitrogen and sulfur;

$R^5$ is hydrogen, alkyl, alkenyl, alkyl(heterocyclo), alkyl-NHCO(alkyl), alkyl-NHCO(aryl), alkyl-NHCO(heterocyclo), alkyl-NHCO(alkylheterocyclo); and

n is an integer of 0 to 2.

3. A compound as recited in Claim 2 wherein

$R^1$ is O-alkyl(aryl), CONH-alkyl, CONH-alkyl(aryl), CONH-alkyl(cycloalkyl);

$R^2$ is hydrogen;

$R^3$ is oxo, hydroxy, alkoxy or NOH;

$R^4$ is hydrogen or alkyl;

$R^5$ is alkyl, alkyl(substituted amino); and

n is an integer of 0 to 2.

4. A compound as recited in Claim 2 which is:

3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, hydrochloride;

3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, hydrochloride;

3,4-Dihydro-6-methoxy-2-[(2-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-methoxy-2-[(3-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-5-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

6-Ethyl-3,4-dihydro-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-(phenylmethoxy)-2-(1-piperidinylmethyl)-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-(2-phenylethoxy)-2-(1-piperidinylmethyl)-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-phenoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-phenyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

2,3-Dihydro-5-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1H-inden-1-one, monohydrochloride;

3,4-Dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-methoxy-2-methyl-2-[(2-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer A, monohydrochloride;

3,4-Dihydro-6-methoxy-2-methyl-2-[(3-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer A, monohydrochloride;

3,4-Dihydro-6-methoxy-2-methyl-2-[(3-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, isomer B, monohydrochloride;

3,4-Dihydro-5-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-2-methyl-6-phenoxy-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-2-methyl-6-phenyl-2-[(4-phenyl-1-piperidinyl)-methyl]-1(2H)-naphthalenone, monohydrochloride;

1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetic acid, methyl ester, monohydrochloride;

trans- and cis-1,2,3,4-Tetrahydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, monohydrochloride

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, isomer A;

1,2,3,4-Tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenol, isomer B monohydrochloride;

(1S)-1,2,3,4-Tetrahydro-1-oxo-N-(1-phenylethyl)-6-(phenylmethoxy)-2-naphthalencarboxamide;

(1R)-1,2,3,4-Tetrahydro-1-oxo-N-(1-phenylethyl)-6-(phenylmethoxy)-2-naphthalencarboxamide;

1-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]carbonyl]-4-phenylpiperidine;

(1R)-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-N-(1-phenylethyl)-2-naphthalenecarboxamide, 1:1 diastereomer mixture;

(1S)-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-N-(1-phenylethyl)-2-naphthalenecarboxamide, 1:1 diastereomer mixture;

1-[[6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-1-oxo-2-naphthalenyl]carbonyl]-4-phenylpiperidine;

trans-1,2,3,4-Tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-6-(phenylmethoxy)-1-naphthalenol, monohydrochloride;

cis-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-1-naphthalenol;

trans-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-1-naphthalenol, single isomer A;

trans-6-([1,1'-Biphenyl]-2-yl)-1,2,3,4-tetrahydro-2-[[[(S)-1-phenylethyl]amino]methyl]-1-naphthalenol, isomer B;

cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[(4-phenyl-1-piperidinyl)]methyl]-1-naphthalenol;

3,4-Dihydro-6-methoxy-2-[2-oxo-2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

1-Phenyl-4-[[1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]piperazine;

1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-[2-(2-pyridinyl)ethyl]-2-naphthaleneacetamide;

1,2,3,4-Tetrahydro-N,N-bis(2-methylpropyl)-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide;

1-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]piperidine;

N-(2,3-Dihydro-1H-inden-2-yl)-1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide;

1-Methyl-4-[[1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]piperazine;

1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(phenylmethyl)-2-naphthaleneacetamide;

1,2,3,4-Tetrahydro-1-oxo-N-methyl-6-(phenylmethoxy)-N-(phenylmethyl)-2-naphthaleneacetamide;

(1S)-1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(1-phenylethyl)-2-naphthaleneacetamide;

(1R)-1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-N-(1-phenylethyl)-2-naphthaleneacetamide;

N-(3,3-Dimethylbutyl)-1,2,3,4-tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthaleneacetamide;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, 1,1-dimethylethyl ester;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-leucine, phenylmethyl ester;

N2-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-phenylalaninamide;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, ethyl ester ;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-leucine, methyl ester;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-phenylalanine, methyl ester;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-valine, methyl ester;

N-[[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]acetyl]-L-serine, phenylmethyl ester;

1,2,3,4-Tetrahydro-6-methoxy-2-(2-(4-phenyl-1-piperidinenyl)-ethyl]-1(2H)-naphthalenol, monohydrochloride;

cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1);

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol;

trans-1,2,3,4-Tetrahydro-6-phenyl-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol;

trans-1,2,3,4-Tetrahydro-6-phenoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol;

trans-2-[2-[Bis(2-methylpropyl)amino]ethyl]-1,2,3,4-tetrahydro--6-(phenylmethoxy)-1-naphthalenol;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(1-piperidinyl)ethyl]-1-naphthalenol;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[methyl(phenylmethyl)amino]ethyl]-1-naphthalenol;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, enantiomer A;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol, enantiomer B;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer B;

cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) ;

cis-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(R)-1-phenylethyl]amino]ethyl]-1-naphthalenol, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) ;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(R)-1-phenylethyl]amino]-1-naphthalenol, isomer A, L-tartrate (1:1) ;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(R)-1-phenylethyl]amino]-1-naphthalenol, isomer B;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer A, L-tartrate (1:1) ;

trans-1,2,3,4-Tetrahydro-6-(phenylmethoxy)-2-[2-[[(S)-1-phenylethyl]amino]-1-naphthalenol, isomer B;

trans-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, diastereomer A;
trans-6-([1,1'-Biphenyl]-2-ylmethoxy)-1,2,3,4-tetrahydro-2-[2-[[(S)-1-phenylethyl]amino]ethyl]-1-naphthalenol, diastereomer B;
3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]- 1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-phenoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-phenyl-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

3.4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(4-pyridinylmethoxy)010(2H)-naphthalenone, dihydrochloride ;

3,4-Dihydro-6-(2-phenylethyl)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone;

6-[(1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-(2-methylpropoxy)-2-[2-oxo-2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(4-pyridinylmethoxy)-1(2H)-naphthalenone, dihydrochloride;

3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-(3-pyridinylmethoxy)-1(2H)-naphthalenone, dihydrochloride;

3,4-Dihydro-6-[(3-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-[(4-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[(4-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-[(2-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-[(3-Chlorophenyl)methoxy]-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[[4-(1-methyletyl)phenyl]methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

4-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile;

3,4-Dihydro-5-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, trifluoroacetate (1:1) ;

3,4-Dihydro-56-(phenylmethoxy)-2-[2-(4-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-(phenylmethoxy)-2-[2-(2-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, isomer A;

3,4-Dihydro-6-(phenylmethoxy)-2-[2-(2-phenyl-1-piperidinyl)-ethyl]-1(2H)-naphthalenone, isomer B;

3,4-Dihydro-6-[(1-phenyl-1H-imidazol-2-yl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-2-[(4-phenyl-1-piperidinyl)ethyl]-6-(2,2,2-trifluoroethoxy)-1(2H)-naphthalenone, monohydrochloride;

3,4-Dihydro-6-[(3-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[(2-methoxyphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[(2-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)naphthalenone;

6-([1,1'-Biphenyl]-4-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-ethoxy-1(2H)-naphthalenone;

3,4-Dihydro-6-[(2-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

2-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile;

4-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzoic acid, methyl ester;

3-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piper-idinyl)ethyl]-2-naphthalenyl]oxy]methyl]benzonitrile;

3,4-Dihydro-6-[(4-nitrophenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[(4-methylphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-6-[(3-methoxyphenyl)methoxy]-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-propoxy-1(2H)-naphthalenone;

3,4-Dihydro-6-(1-methylethoxy)-2-[2-(4-phenyl-1-piper-idinyl)ethyl]-1(2H)-naphthalenone;

3,4-Dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-6-[(2-propenyl)oxy]-1(2H)-naphthalenone;

3,4-Dihydro-6-(1-phenylethoxy)-2-[2-(4-phenyl-1-piper-idinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

6-(1H-Benzimidazol-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, dihydrochloride;

6-([1,1'-Biphenyl]-3-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-(Cyclopropylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-proline, 1,1-dimethylethyl ester;

2-[2-[Cyclohexyl(1-methylethyl)amino]ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone;

2-[2-(2-Ethyl-1-piperidinyl)ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone;

3,4-Dihydro-2-[2-[(S)-2-(methoxymethyl)-1-pyrrolidinyl]ethyl]-6-(phenylmethoxy)-1(2H)-naphthalenone, monohydrochloride;

1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-proline, phenylmethyl ester;

1-[2-[1,2,3,4-Tetrahydro-1-oxo-6-(phenylmethoxy)-2-naphthalenyl]ethyl]-L-prolinamide;

6-Ethoxy-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, monohydrochloride;

2-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-6-(phenylmethoxy)-1(2H)-naphthalenone;

(Z)- and (E)-3,4-Dihydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime;

3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime, monohydrochloride;

3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime;

3,4-Dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone hydrazone;

N-Methyl-2-[3,4-dihydro-6-methoxy-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenylidene]-hydrazinecarboxamide;

(E)-6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime;

(E)-6-([1,1'-Biphenyl]-2-ylmethoxy)-3,4-dihydro-2-[2-(1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime;

(E)-6-Ethoxy-3,4-dihydro-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone, oxime;

(E)-3,4-Dihydro-2-methyl-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime;

(Z)-3,4-Dihydro-2-methyl-6-(phenylmethoxy)-2-[(4-phenyl-1-piperidinyl)methyl]-1(2H)-naphthalenone, oxime;

trans-N-[1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenyl]acetamide;

cis-N-[1,2,3,4-tetrahydro-6-methoxy-2-methyl-2-[(4-phenyl-1-piperidinyl)methyl]-1-naphthalenyl]acetamide;

1',2',3',4'-Tetrahydro-6'-methoxy-2'-[2-(4-phenyl-1-piperidinyl)ethyl]spiro[imidazolidine-4,1'(2'H)-naphthalene]-2,5-dione;

1',2',3',4'-Tetrahydro-6'-(phenylmethoxy)-2'-[2-(4-phenyl-1-piperidinyl)ethyl]spiro[imidazolidine-4,1'(2'H)-naphthalene]-2,5-dione, isomer A;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, methyl ester;

5,6,7,8-Tetrahydro-5-oxo-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-pentyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

1-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]piperidine;

5,6,7,8-Tetrahydro-N-(1H-imidazol-2-yl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, dihydrochloride;

2-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]acetic acid, ethyl ester;

4-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]-1-piperidinecarboxylic acid, ethyl ester;

5,6,7,8-Tetrahydro-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-([1,1-Biphenyl]2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-5-oxo-N-methyl-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-(1-methylethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-[3,5-Bis(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-N-(3,3-dimethylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

4-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]benzoic acid, methyl ester;

5,6,7,8-Tetrahydro-N-(2-methoxyphenyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-N-(3-pyridinyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-N-(3,4-dimethyl-5-isoxazolyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-N-[2-(1-methylethyl)phenyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:1.37) hydrochloride;

N-(3-Chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:2.07) hydrochloride;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-pyridinyl)-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, 1-phenylhydrazide, dihydrochloride;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-pyridinyl)-2-naphthalenecarboxylic acid, 2-phenylhydrazide, hydrochloride;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-methoxy-N-methyl-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-([1,1-Biphenyl]-3-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(1H-pyrrol-1-yl)-2-naphthalenecarboxamide, monohydrochloride;

5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-(2-phenoxyphenyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

N-(3,5-Dimethoxyhenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, monohydrochloride;

N-(3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide, monohydrochloride;

N-(1,1-Biphenyl]-2-ylmethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, (1:1.07) hydrochloride;

(3-phenylpropyl)-2-naphthalenecarboxamide
5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(4-phenylbutyl)-2-naphthalenecarboxamide;

N-[2-Cyclohexen-1-yl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-[2-(3,4-Dimethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-[2,2-Diphenylethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-[2,3-Dihydro-1H-inden-2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-[2-(1-naphthalenyl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, hydrochloride;

5,6,7,8-Tetrahydro-N-[2-(2-naphthalenyl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-[(2,2-Dimethylcyclopentyl)methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

trans-5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylcyclopropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-(1-naphthalenylmethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(S)-2-phenylcyclopropyl)-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(R)-2-phenylcyclopropyl)-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-[(R)-1-(hydroxymethyl)-3-methylbutyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide;

5,6,7,8-Tetrahydro-N-[(S)-1-(hydroxymethyl)-3-methylbutyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[2-(2-thienyl)ethyl]-2-naphthalenecarboxamide;

N-[(1-(4-Chlorophenyl)cyclopropyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalene-carboxamide;

N-[2-(4-Dibenzofuranyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-(3-hydroxy-2,3-diphenylpropyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

cis-5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylcyclopropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-(2,2,3,3,3-pentafluoropropyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-(2-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

5,6,7,8-Tetrahydro-N-(3-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

5,6,7,8-Tetrahydro-N-(1-methylbutyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-[(tetrahydro-2-furanyl)methyl]-2-naphthalenecarboxamide, trifluoroacetate;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(2-phenylpropyl)-2-naphthalenecarboxamide, trifluoroacetate;

5,6,7,8-Tetrahydro-N-(2-hydroxy-2-phenylethyl)-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

N-[2-(2-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

N-[2-(4-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-6-naphthalenecarboxamide, trifluoroacetate;

N-[2-(3-Fluorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

N-[2-(4-Chlorophenyl)ethyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-[2-(1H-indol-3-yl)ethyl]-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-(3,3-Diphenylpropyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-[2-(4-phenoxyphenyl)ethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

3,4-Dihydro-6-methoxy-2-[3-(4-phenyl-1-piperidinyl)propyl]-1(2H)-naphthalenone, monohydrochloride;

(E)-3,4-Dihydro-6-methoxy-2-[(4-phenyl-1-piperidinyl)propyl]-1(2H)-naphthalenone, oxime;

5,6,7,8-Tetrahydro-5-(hydroxyimino)-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-(hydroxyimino)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxylic acid, methyl ester;

5,6,7,8-Tetrahydro-5-(hydroxyimino)-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-(hydroxyimino)-6-[2-(4-phenyl)-1-piperidinyl)ethyl]-2-naphthalenecarboxamide;

2-[[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]carbonyl]amino]acetic acid;

1,2,3,4-Tetrahydro-6-(hydroxymethyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenol

cis-5,6,7,8-Tetrahydro-5-hydroxy-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenecarboxamide, trifluoroacetate;

3,4-Dihydro-6-(phenylacetyl)-2-[2-(4-phenyl-1-piperidinyl)ethyl]-1(2H)-naphthalenone;

5,6,7,8-Tetrahydro-5-oxo-N-(phenylmethyl)-6-[2-(4- phenyl-1-piperidinyl)ethyl]-2-naphthaleneacetamide;

N-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzeneacetamide

3,3-Dimethyl-N-[[5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]butanamide
and;

N-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]methyl]benzeneacetamide;

3,3-Dimethyl-N-[[5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-2-naphthalenyl]butanamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-2-naphthalene-carboxamide

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-methoxy-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5-(hexyloxy)-5,6,7,8-tetrahydro-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide;

N-[[3,5 Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalene-carboxamide;

5,6,7,8-Tetrahydro-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-pentyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-([1,1'-Biphenyl]-2-yl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

1-[[5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenyl]carbonyl]piperidine, (E)-2-butenedioate (1:1) ;

5,6,7,8-Tetrahydro-5-oxo-N-(2-phenylethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-[(R)-1-phenylethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-[(S)-1-phenylethyl]-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-(3,5-Dimethoxyphenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-(2,5-Dimethoxyphenyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-([1,1'-Biphenyl]-2-ylmethyl)-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-(3,5-Bis(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

N-([1,1'-Biphenyl]-3-yl))-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-methyl-5-oxo-N-phenyl-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-N-(2-phenoxyphenyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-N-(3-phenylpropyl)-1-naphthalenecarboxamide;

N-[(2,2-Dimethylcyclopentyl)methyl]-5,6,7,8-tetrahydro-5-oxo-6-[2-(4-phenyl-1-piperidinyl)ethyl]-1-naphthalenecarboxamide;

5,6,7,8-Tetrahydro-N-phenyl-N-(phenylmethyl)-6-[2-(4-phenyl-1-piperidinyl)ethyl]-5-oxo-1-naphthalenecarboxamide;

6-Hexyl-5,6,7,8-tetrahydro-5-oxo-N-(2-phenylethyl)-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide;

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide;

N-[[2,2-Dimethylcyclopentyl)methyl]-6-hexyl-5,6,7,8-tetrahydro-5-oxo-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-2-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-propyl-2-naphthalenecarboxamide;

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-2-naphthalenecarboxamide;

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-1-naphthalenecarboxamide;

N-[[3,5-Bis(trifluoromethyl)phenyl]methyl]-5,6,7,8-tetrahydro-5-oxo-6-propyl-1-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-oxo-6-(2-propenyl)-1-naphthalenecarboxamide;

N-(3,3-Dimethylbutyl)-5,6,7,8-tetrahydro-5-hydroxy-2-naphthalenecarboxamide; or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02338

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :514/278, 821; 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278, 821; 546/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON-LINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5,439,914 A (CLAREMON et al.) 08 August 1995, see the entire document. | 1-4 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>30 MARCH 1998 | Date of mailing of the international search report<br>05 JUN 1998 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>KEVIN E. WEDDINGTON<br>Telephone No. (703) 308-1235 |

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/02338

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6): A61K 31/44; C07D 491/107

PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
Bureau international

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets 6 : C07C 233/05, A61K 7/48

A1

(11) Numéro de publication internationale: WO 98/56754

(43) Date de publication internationale: 17 décembre 1998 (17.12.98)

(21) Numéro de la demande internationale: PCT/FR98/01077

(22) Date de dépôt international: 28 mai 1998 (28.05.98)

(30) Données relatives à la priorité:
97/07241 11 juin 1997 (11.06.97) FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: L'OREAL [FR/FR]; 14, rue Royale, F–75008 Paris (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants *(US seulement)*: PHILIPPE, Michel [FR/FR]; 34, rue Pierre et Marie Curie, F–91320 Wissous (FR). SEMERIA, Didier [FR/FR]; 10, allée des Lavandières, F–77181 Courtry (FR).

(74) Mandataire: DODIN, Catherine; L'Oréal D.P.I., 90, rue du Général Roguet, F–92583 Clichy Cedex (FR).

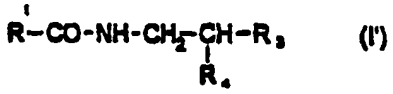
(81) Etats désignés: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, brevet ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Publiée**

*Avec rapport de recherche internationale.*

(54) Title: COSMETIC COMPOSITION COMPRISING AN AMIDE AND NOVEL AMIDES

(54) Titre: COMPOSITION COSMETIQUE COMPRENANT UN AMIDE ET NOUVEAUX AMIDES



(I')

(57) Abstract

The invention concerns a composition, in particular a cosmetic composition, comprising at least a powder substance and a branched amide used as dispersion agent. The invention also concerns novel branched amides of formula (I').

(57) Abrégé

L'invention concerne une composition, notamment cosmétique, comprenant au moins une matière pulvérulente et un amide ramifié utilisé comme agent de dispersion. L'invention concerne aussi de nouveaux amides ramifiés de formule (I').

*UNIQUEMENT A TITRE D'INFORMATION*

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

| | |
|---|---|
| AL | Albanie |
| AM | Arménie |
| AT | Autriche |
| AU | Australie |
| AZ | Azerbaïdjan |
| BA | Bosnie-Herzégovine |
| BB | Barbade |
| BE | Belgique |
| BF | Burkina Faso |
| BG | Bulgarie |
| BJ | Bénin |
| BR | Brésil |
| BY | Bélarus |
| CA | Canada |
| CF | République centrafricaine |
| CG | Congo |
| CH | Suisse |
| CI | Côte d'Ivoire |
| CM | Cameroun |
| CN | Chine |
| CU | Cuba |
| CZ | République tchèque |
| DE | Allemagne |
| DK | Danemark |
| EE | Estonie |
| ES | Espagne |
| FI | Finlande |
| FR | France |
| GA | Gabon |
| GB | Royaume-Uni |
| GE | Géorgie |
| GH | Ghana |
| GN | Guinée |
| GR | Grèce |
| HU | Hongrie |
| IE | Irlande |
| IL | Israël |
| IS | Islande |
| IT | Italie |
| JP | Japon |
| KE | Kenya |
| KG | Kirghizistan |
| KP | République populaire démocratique de Corée |
| KR | République de Corée |
| KZ | Kazakstan |
| LC | Sainte-Lucie |
| LI | Liechtenstein |
| LK | Sri Lanka |
| LR | Libéria |
| LS | Lesotho |
| LT | Lituanie |
| LU | Luxembourg |
| LV | Lettonie |
| MC | Monaco |
| MD | République de Moldova |
| MG | Madagascar |
| MK | Ex-République yougoslave de Macédoine |
| ML | Mali |
| MN | Mongolie |
| MR | Mauritanie |
| MW | Malawi |
| MX | Mexique |
| NE | Niger |
| NL | Pays-Bas |
| NO | Norvège |
| NZ | Nouvelle-Zélande |
| PL | Pologne |
| PT | Portugal |
| RO | Roumanie |
| RU | Fédération de Russie |
| SD | Soudan |
| SE | Suède |
| SG | Singapour |
| SI | Slovénie |
| SK | Slovaquie |
| SN | Sénégal |
| SZ | Swaziland |
| TD | Tchad |
| TG | Togo |
| TJ | Tadjikistan |
| TM | Turkménistan |
| TR | Turquie |
| TT | Trinité-et-Tobago |
| UA | Ukraine |
| UG | Ouganda |
| US | Etats-Unis d'Amérique |
| UZ | Ouzbékistan |
| VN | Viet Nam |
| YU | Yougoslavie |
| ZW | Zimbabwe |

# Composition cosmétique comprenant un amide et nouveaux amides

La présente invention concerne une nouvelle composition, notamment cosmétique, comprenant des matières pulvérulentes et des amides particuliers. L'invention concerne également l'utilisation de certains amides comme agent dispersant de matières pulvérulentes, ainsi qu'un procédé de dispersion de matières pulvérulentes.

Il est connu d'employer dans les compositions cosmétiques des matières pulvérulentes telles que des pigments ou des charges dans le but notamment de conférer à ces compositions une couleur désirée. Certains pigments d'oxydes métalliques, comme le dioxyde de titane, sont également utilisés pour leurs bonnes propriétés anti-UV connues. Toutefois, l'incorporation de ces matières pulvérulentes dans les compositions cosmétiques n'est pas toujours facile à mettre en œuvre. En effet, on observe fréquemment l'apparition d'agglomérats et les pigments ont souvent tendance à sédimenter au cours du temps : la dispersion des pigments dans la composition n'est alors plus homogène. La sédimentation des pigments ne permet plus de conserver l'uniformité de la couleur de la composition, notamment lors de son application sur la peau. Cette sédimentation peut également engendrer une diminution sensible de l'efficacité de la protection solaire conférée par les pigments possédant une propriété anti-UV.

Pour empêcher l'agglomération et/ou la sédimentation des pigments, il a été proposé d'utiliser des agents de dispersion, et notamment des esters d'alkyle ramifiés. Par exemple, les brevets US-A-5476643 et US-A-5516506 décrivent l'emploi d'esters de néopentylglycol pour favoriser la dispersion des pigments. Selon la demande WO 94/18940, il est aussi connu d'améliorer la dispersion des pigments d'oxyde de titane en utilisant des composés organiques ramifiés tels que des esters, des éthers, des hydrocarbures ou des silicones, et en particulier le néopentanoate d'octyldodécyle.

Bien que ces agents dispersants décrits dans l'état de la technique permettent de mettre en dispersion les pigments couramment utilisés dans le domaine cosmétique, la stabilité dans le temps de ces dispersions n'est toutefois pas satisfaisante. En effet, on constate qu'après plusieurs heures de stockage, voire même plusieurs jours, la dispersion de pigments ne conserve pas son homogénéité car les pigments sédimentent au cours du temps.

Par ailleurs, il est connu par le brevet US-A-5162315 et la demande de brevet JP-A-62-215537, d'utiliser des amides comportant au moins deux chaînes alkyle pour améliorer le pénétration cutanée d'agents actifs pharmaceutiques. Dans la demande WO 88/04167, des amides comportant deux chaînes alkyle sont employés dans une composition antisolaire ou hydratante, sous forme d'émulsion, pour conférer à la composition une résistance à l'humidité.

La présente invention a pour but de permettre la préparation et l'obtention d'une composition qui comprend de matières pulvérulentes dispersées de manière homogène et qui est stable dans le temps.

La Demanderesse a découvert, de façon inattendue et surprenante, qu'en utilisant certains amides ramifiés, on pouvait obtenir une dispersion de matières pulvérulents parfaitement stable. De plus, la stabilité de la dispersion ainsi obtenue peut être conservée pendant plus d'une semaine, voire pendant plus d'un mois.

Aussi, l'invention concerne une composition comprenant au moins une matière pulvérulente et au moins un amide de formule (I) suivante :

$$R^1\text{-CO-NH-}R^2 \quad (I)$$

dans laquelle $R^1$ et $R^2$, indépendamment l'un de l'autre, désignent un radical alkyle ramifié, saturé ou insaturé, comprenant de 3 à 30 atomes de carbone. De préférence, $R^1$ et $R^2$, indépendamment l'un de l'autre, désignent un radical alkyle ramifié saturé ayant de 3 à 20 atomes de carbone. Plus préférentiellement, $R^1$ comporte de 3 à 10 atomes de carbone et $R^2$ comporte de 10 à 20 atomes de carbone.

Avantageusement, $R^2$ désigne un radical ramifié de formule (II) :

$$-CH_2-\underset{\displaystyle R_4}{\underset{|}{CH}}-R_3 \qquad (II)$$

dans laquelle $R_3$ et $R_4$, indépendamment l'un de l'autre, désignent un radical alkyle linéaire comprenant de 1 à 27 atomes de carbone, sous réserve que le nombre total d'atome de carbone du radical de formule (II) soit inférieur ou égal à 30. De préférence, $R_3$ et $R_4$, indépendamment l'un de l'autre, comportent de 2 à 12 atomes de carbone, et plus préférentiellement de 2 à 10 atomes de carbone.

Comme groupement $R^1$, on peut citer par exemple les groupements tert-butyle et 2,4,4-triméthyl pentyle.
Comme groupement $R^2$, on peut notamment citer les groupements 2-octyl dodécyl et 2-butyl octyl.

Parmi les composés préférés correspondant à la formule générale (I), on peut notamment citer :
- le N-néopentanoyl-2-octyl-dodécylamine,
- le N-néopentanoyl-2-butyl-octylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-octyl-dodécylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-butyl-octylamine.

Les composés de formule (I) sont de préférence présents en une teneur allant de 0,1% à 50 % en poids, par rapport au poids total de la composition, et mieux de 2 à 20 %.

Les matières pulvérulentes présentes dans la composition peuvent être choisies parmi les pigments, les nacres, et/ou les charges. Ils sont de préférence présents à raison de 0,1 à 80 % en poids par rapport au poids total de la composition.

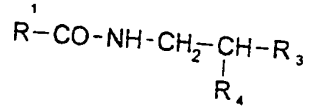
Parmi les pigments, on peut citer les pigments minéraux tels que les oxydes de titane, de zinc, de fer, de zirconium, de cérium ou leurs mélanges. On peut également utiliser les nanopigments de ces oxydes métalliques qui sont connus pour leur propriété anti-UV. Ces nanopigments sont utilisés de façon connue dans les compositions anti-solaires. On entend par "nanopigments" des pigments dont la taille moyenne des particules primaires n'excède pas 100 nm, cette taille étant de préférence comprise entre 5 nm et 100 nm, et plus préférentiellement encore comprise entre 10 et 50 nm. De tels nanopigments d'oxydes métalliques, enrobés ou non enrobés, sont des produits connus de l'homme de l'art et sont en particulier décrits dans la demande de brevet EP-A- 0 518 773, dont l'enseignement est, à cet égard, inclu à titre de référence dans la présente description.

Comme pigments minéraux, on peut également citer l'oxyde de chrome, le violet de manganèse, le bleu outremer, l'hydrate de chrome et le bleu ferrique. Les pigments organiques peuvent être choisis parmi le noir de carbone, les pigments de type D & C, et les laques à base de carmin de cochenille.

Les nacres peuvent être choisies parmi les pigments nacrés blancs tels que le mica recouvert d'oxyde de titane ou d'oxychlorure de bismuth, les pigments nacrés colorés tels que le mica titane recouvert d'oxydes de fer, le mica titane avec notamment du bleu ferrique ou de l'oxyde de chrome, le mica titane avec un pigment organique du type précité ainsi que les pigments nacrés à base d'oxychlorure de bismuth.

Les charges peuvent être minérales ou organiques, lamellaires ou sphériques. On peut citer le talc, le mica, la silice, le kaolin, les poudres de Nylon, de poly-β-alanine et de polyéthylène, le Téflon, la lauroyl-lysine, l'amidon, le micatitane, la nacre naturelle, le nitrure de bore, les poudres de polymères de tétrafluoroéthylène, les microsphères creuses telles que l'Expancel (Nobel Industrie), le polytrap (Dow Corning) et les microbilles de résine de silicone (Tospearls de Toshiba, par exemple), les oxydes de zinc et de titane, le carbonate de calcium précipité, le carbonate et l'hydrocarbonate de magnésium, l'hydroxyapatite, les microsphères de silice creuses (SILICA BEADS de MAPRECOS), les microcapsules de verre ou de céramique; les savons métalliques dérivés d'acides organiques carboxyliques ayant de 8 à 22 atomes de carbone, de préférence de 12 à 18 atomes de carbone, par exemple le stéarate de zinc, de magnésium ou de lithium, le laurate de zinc, le myristate de magnésium.

L'invention a également pour objet les amides de formule (I') suivante :



(I')

dans laquelle

- $R^1$ désigne un radical alkyle ramifié, saturé ou insaturé, comprenant de 3 à 30 atomes de carbone,
- $R_3$ et $R_4$, indépendamment l'un de l'autre, désignent un radical alkyle linéaire comprenant de 1 à 27 atomes de carbone, sous réserve que le nombre total d'atome de carbone du radical $-CH_2-CH(R_3)(R_4)$ de la formule (I') soit inférieur ou égal à 30.

De préférence, $R^1$, $R_3$ et $R_4$ ont les significations préférées mentionnées précédemment pour les composés de formule (I).

Ces composés se présentent généralement sous forme de liquide huileux. On a donc constaté que la dispersion de matières pulvérulentes dans les amides selon l'invention était meilleure, plus homogène et plus stable dans le temps que la dispersion de ces mêmes matières pulvérulentes dans les huiles de l'art antérieur.

Le mélange de matières pulvérulentes et d'amides ramifiés préalablement préparé peut être introduit par exemple dans un support acceptable pour l'application envisagée, notamment dans un support cosmétiquement acceptable.

On peut encore introduire lesdits amides ramifiés et les matières pulvérulentes séparément, soit dans une composition notamment cosmétique préalablement préparée, soit directement lors du mélange de tous les constituants de la composition notamment cosmétique, selon des procédés bien connus de l'homme du métier .

La composition selon l'invention peut comprendre également au moins une huile, notamment choisie parmi les huiles végétales, animales, minérales ou synthétiques. Bien entendu, l'homme du métier veillera à employer des huiles qui ne nuisent pas à la bonne dispersion des matières pulvérulentes dans la composition, dans des quantités acceptables pour ne pas altérer ladite dispersion.

Selon une réalisation particulière de la composition de l'invention, la composition comprend comme unique huile un composé de formule (I) tel que défini précédemment.

La composition peut aussi comprendre d'autres corps gras comme les cires, qui peuvent être choisies parmi les cires animales, fossiles, végétales, minérales ou de synthèse connues en soi.

Avantageusement, la composition selon l'invention peut comprendre un support cosmétiquement acceptable.

La composition de l'invention peut également contenir au moins un additif choisi parmi les épaississants, les tensioactifs, les parfums, les conservateurs, les filtres solaires, les protéines, les vitamines, les polymères, et tout autre additif classiquement utilisé dans le domaine cosmétique. La quantité précise de chaque additif est déterminée facilement par l'homme de l'art selon sa nature et sa fonction.

Bien entendu, l'homme du métier veillera à choisir ce ou ces éventuels additifs et/ou leurs quantités de manière telle que les propriétés avantageuses, et notamment de dispersion des matières pulvérulentes, attachées intrinsèquement aux composés de formule (I) conforment à l'invention ne soient pas, ou substantiellement pas, altérées par la ou les adjonctions envisagées.

Les procédés de fabrication des compositions selon l'invention ne diffèrent en rien des procédés classiquement utilisés, notamment en cosmétique, et parfaitement connus de l'homme de l'art.

La composition selon l'invention peut se présente sous la forme d'une dispersion, d'une émulsion, notamment une émulsion eau-dans-huile ou huile-dans-eau, ou bien encore sous la forme d'une pâte souple.

Les compositions cosmétiques selon l'invention peuvent se présenter sous forme de composition de maquillage, de composition de soin de la peau, de composition capillaire ou de composition anti-solaire.

Les compositions de maquillage peuvent être sous la forme de fard à paupières, de fard à joues, d'eye-liner, de fond de teint, de blush, de mascara, de rouge à lèvres, de stick de soin des lèvres, de composition anti-cernes, de crème teintée.

Les compositions capillaires peuvent se présenter sous forme de shampooing, de lotion, de gel, d'émulsion, de dispersion vésiculaire non ionique, de laque pour cheveux et constituer par exemple une composition à rincer, à appliquer avant ou après shampooing, avant ou après coloration ou décoloration, avant, pendant ou après permanente ou défrisage, une lotion ou un gel coiffants ou traitants, une lotion ou un gel pour le brushing ou la mise en plis, une composition de permanente ou de défrisage, de coloration ou décoloration des cheveux.

L'invention concerne également l'utilisation d'un amide de formule (I) tel que défini précédemment comme agent de dispersion de matières pulvérulentes. On entend par agent de dispersion un composé apte à favoriser la dispersion desdites matières pulvérulentes.

L'invention a aussi pour objet un procédé de dispersion de matières pulvérulentes caractérisé par le fait que lesdites matières pulvérulentes sont dispersées dans une composition comprenant au moins un amide de formule (I) tel que défini précédemment.

On va maintenant donner des exemples illustrant la présente invention sans toutefois la limiter.

**Exemple 1** : Préparation du N-néopentanoyl-2-butyl-octylamine

10,4 g d'acide pivalique et 17,2 g de 2-butyl-octylamine ont été mélangés dans le tube de l'appareil micro-ondes (Maxidigest ™ MX 350 de la société PROLABO; fréquence 2450 ± 50 MHz, puissance modulable 300 W). Après une irradiation d'environ 1 heure à 160 °C ± 10 °C, le mélange réactionnel a été solubilisé dans de l'heptane puis purifié sur silice. On a obtenu 19 g de l'amide souhaité.

Le spectre RMN $^1H$ est conforme à la structure attendue.

Analyse élémentaire : $C_{13}\ H_{37}\ N\ O$

| | C % | H % | N % | O % |
|---|---|---|---|---|
| **Calculé** | 75,84 | 13,01 | 5,20 | 5,95 |
| **Trouvé** | 75,88 | 12,93 | 5,12 | 6,18 |

**Exemple 2** : Préparation du N-néopentanoyl-2-octyl-dodécylamine

62 ml de chlorure de pivaloyle ont été solubilisés dans 180 ml d'heptane puis additionnés à 150 g de 2-octyl-dodécylamine à une température de 60 °C. Après addition de 70 ml de triéthylamine, le milieu réactionnel a été agité pendant 2 heures, puis purifié sur silice. On a ainsi obtenu 118 g de l'amide souhaité.

Le spectre RMN $^1H$ est conforme à la structure attendue.

Analyse élémentaire : $C_{26}$ $H_{42}$ N O

| | C % | H % | N % | O % |
|---|---|---|---|---|
| **Calculé** | 78,67 | 13,47 | 3,67 | 4,19 |
| **Trouvé** | 78,54 | 13,40 | 3,63 | 4,25 |

**Exemple 3** : Préparation du N-(3,5,5-triméthyl-hexanoyl)-2-octyl-dodécylamine

3,6 g d'acide 3,5,5-triméthyl hexanoïque et 6,8 g de 2-octyl-dodécylamine ont été mélangés dans le tube de l'appareil micro-ondes (Maxidigest ™ MX 350 de la société PROLABO; fréquence 2450 ± 50 MHz, puissance modulable 300 W). Après une irradiation d'environ 50 minutes à 170 °C ± 10 °C, le mélange réactionnel a été solubilisé dans de l'heptane puis purifié sur silice. On a obtenu 7 g de l'amide souhaité.

Le spectre RMN $^1H$ est conforme à la structure attendue.

Analyse élémentaire : $C_{29}$ $H_{59}$ N O

| | C % | H % | N % | O % |
|---|---|---|---|---|
| **Calculé** | 79,63 | 13,50 | 3,20 | 3,66 |
| **Trouvé** | 79,75 | 13,32 | 3,16 | 3,93 |

**Exemple 4** : Préparation du N-(3,5,5-triméthyl-hexanoyl)-2-butyl-octylamine

29,2 g d'acide 3,5,5-triméthyl hexanoïque et 34,2 g de 2-butyl-octylamine ont été mélangés dans un récipient ouvert en pyrex placé dans un four micro-ondes (MENUMASTER ™ 3100 i; fréquence 2450, puissance à 30 % de 1400 W). Après 6 irradiations d'environ 5 minutes (pour chaque irradiation), le mélange réactionnel a été solubilisé dans de l'heptane puis purifié sur silice. On a obtenu 46 g (77 %) de l'amide souhaité.

Le spectre RMN $^1H$ est conforme à la structure attendue.

Analyse élémentaire : $C_{21}$ $H_{42}$ N O

| | C % | H % | N % | O % |
|---|---|---|---|---|
| **Calculé** | 77,54 | 13,23 | 4,31 | 4,92 |
| **Trouvé** | 77,45 | 13,06 | 4,23 | 5,12 |

**Exemple 5** : Exemples comparatifs sur les propriétés de dispersion

On a mesuré les vitesse de sédimentation d'un pigment dispersé dans différentes huiles.

Protocole :
On a préparé un mélange de pigment et d'huile comprenant 5 % de pigment. Ce mélange a été agité pendant 20 heures à 30 °C. On a ensuite prélevé 10 ml de la dispersion obtenue après l'agitation dans un tube gradué. Puis on a mesuré le volume de pigment déposé au fond du tube (culot) en fonction du temps. On a déduit alors le volume du surnageant restant dans le tube.

Le pigment utilisé est de l'oxyde de fer rouge vendu sous la dénomination "SICOMET BRUN ZP 3569" par la société BASF.

Résultats :

On a reporté le volume de surnageant (en ml), pour chaque huile testée, mesuré au cours du temps jusqu'à environ 200 heures.

On a obtenu les résultats suivants :

a) huiles selon l'invention :

| **Heures** | **0** | **1** | **9** | **24** | **49** | **72** | **147** | **201** |
|---|---|---|---|---|---|---|---|---|
| **Huile n° 1** | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| **Huile n° 2** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Huile n° 3** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Huile n° 4** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

Huile n°1 : composé de l'exemple 1
Huile n° 2 : composé de l'exemple 2
Huile n° 3 : composé de l'exemple 3
Huile n° 4 : composé de l'exemple 4

On a constaté que le volume du surnageant est constant avec les 4 huiles ramifiées selon l'invention. Ces huiles permettent donc d'obtenir une dispersion stable du pigment.

b) huiles ne faisant pas partie de l'invention :

| Heures | 0 | 6 | 12 | 25 | 50 | 100 | 150 | 200 |
|---|---|---|---|---|---|---|---|---|
| Huile A | 9 | 7 | 7 | 6,5 | 6,5 | 6,5 | 6,5 | 6,5 |
| Huile B | 10 | 9,9 | 9,8 | 9,5 | 9 | 7,5 | 4 | 3,8 |
| Huile C | 8 | 5,2 | 4,8 | 4,8 | 4,8 | 4,8 | 4,8 | 4,8 |
| Huile D | 6,5 | 4 | 3,9 | 3,8 | 3,8 | 3,8 | 3,8 | 3,8 |
| Huile E | -- | 9 | 6,5 | 2,75 | 2,4 | 2 | 1,9 | 1,8 |

Huile A : Huile de Parléam
Huile B : Huile de ricin
Huile C : Huile de silicone (SILICONE OIL L-45 10 cst de UNION CARBIDE)
Huile D : Néopentanoate d'octyle dodécyle
Huile E : Huile de silicone phénylée (DOW CORNING 556 FLUID COSMETIC de DOW CORNING)

On a constaté qu'avec les 5 huiles ne faisant pas partie de l'invention, le volume de surnageant diminue au bout de 6 heures, la diminution étant même importante après 200 heures. Les dispersions de pigment dans ces huiles ne sont donc pas stables au cours du temps, contrairement aux dispersions dans les huiles selon l'invention.

**Exemple 6 :**

On a préparé une émulsion huile-dans-eau ayant la composition suivante :

| | | |
|---|---|---|
| - mélange d'alcool cétylstéarylique et d'alcool cétylstéarylique oxyéthyléné à 33 moles d'oxyde d'éthylène (80/20) ("DEHSCONET 390" de la société TENSIA) | | 7 g |
| - mélange de mono et distéarate de glycérol ("CERASYNTH SD" de la société ISP) | | 2 g |
| - alcool cétylique | | 1,5 g |
| - polydiméthylsiloxane ("DC200 Fluid" De DOW CORNING) | | 1,5 g |
| - composé de l'exemple 2 | | 10 g |
| - Nanopigment d'oxyde de titane (MT 100 T de la société TAYCA) | | 5 g |
| - glycérine | | 20 g |
| - conservateurs | qs | |
| - eau déminéralisée | qsp | 100g |

On a obtenu une crème fluide dans laquelle les nanopigments d'oxyde de titane sont dispersés de façon homogène dans la composition. Cette crème est utilisée comme composition anti-solaire pour le visage.

## REVENDICATIONS

1. Composition comprenant au moins une matière pulvérulente caractérisée par le fait qu'elle comprend au moins un amide de formule (I) suivante :

$$R^1\text{-CO-NH-}R^2 \quad (I)$$

dans laquelle $R^1$ et $R^2$, indépendamment l'un de l'autre, désignent un radical alkyle ramifié, saturé ou insaturé, comprenant de 3 à 30 atomes de carbone.

2. Composition selon la revendication 1, caractérisée par le fait que $R^1$ et $R^2$ désignent, indépendamment l'un de l'autre, un radical alkyle saturé ayant de 3 à 20 atomes de carbone.

3. Composition selon l'une des revendications précédentes, caractérisée par le fait que $R^1$ désigne un radical alkyle saturé ayant de 3 à 10 atomes de carbone.

4. Composition selon l'une des revendications 1 et 2, caractérisée par le fait que $R^2$ désigne un radical ramifié de formule (II) :

$$-CH_2-\underset{\displaystyle R_4}{\underset{|}{CH}}-R_3 \qquad (II)$$

dans laquelle $R_3$ et $R_4$, indépendamment l'un de l'autre, désignent un radical alkyle linéaire comprenant de 1 à 27 atomes de carbone, sous réserve que le nombre total d'atome de carbone du radical de formule (II) soit inférieur ou égal à 30.

5. Composition selon la revendication 4, caractérisée par le fait que $R^3$ et $R^4$, indépendamment l'un de l'autre, comportent de 2 à 12 atomes de carbone, et de préférence, de 2 à 10 atomes de carbone.

6 . Composition selon l'une quelconque des revendications précédentes, caractérisée par le fait que l'amide est choisi dans le groupe formé par :
- le N-néopentanoyl-2-octyl-dodécylamine,
- le N-néopentanoyl-2-butyl-octylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-octyl-dodécylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-butyl-octylamine.

7. Composition selon l'une quelconque des revendications précédentes, caractérisée par le fait que la matière pulvérulente est choisie dans le groupe formé par les pigments, les charges et les nacres.

8. Composition selon l'une quelconque des revendications précédentes, caractérisée par le fait que l'amide de formule (I) est présent en une teneur allant de 0,1% à 50 % en poids par rapport au poids total de la composition, et mieux de 2 à 20 %.

9 . Composition selon l'une quelconque des revendications précédentes, caractérisée par le fait que la matière pulvérulente est présente en une teneur allant de 0,1% à 80 % en poids, par rapport au poids total de la composition.

10. Composition selon l'une quelconque des revendications précédentes, caractérisée par le fait qu'elle comprend un support cosmétiquement acceptable.

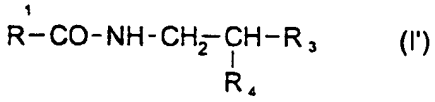
11. Composition cosmétique selon la revendication 10, caractérisée par le fait qu'elle se présente sous la forme d'une dispersion, d'une émulsion ou d'une pâte souple.

12. Composition cosmétique selon la revendication 10 ou 11, caractérisée par le fait que la composition se présente sous la forme d'une composition de maquillage, d'une composition de soin de la peau, d'une composition capillaire, d'une composition anti-solaire.

13. Utilisation d'un amide de formule (I) tel que défini dans l'une des revendications 1 à 6 comme agent de dispersion de matières pulvérulentes.

14. Procédé de dispersion de matières pulvérulentes caractérisé par le fait que lesdites matières pulvérulentes sont dispersées dans une composition comprenant au moins un amide de formule (I) tel que défini dans l'une des revendications 1 à 6.

15. Composés de formule (I') :



(I')

dans laquelle

- $R^1$ désigne un radical alkyle ramifié, saturé ou insaturé, comprenant de 3 à 30 atomes de carbone,
- $R_3$ et $R_4$, indépendamment l'un de l'autre, désignent un radical alkyle linéaire comprenant de 1 à 27 atomes de carbone, sous réserve que le nombre total d'atome de carbone du radical $-CH_2-CH(R_3)(R_4)$ de la formule (I') soit inférieur ou égal à 30.

16. Composés selon la revendication 15, caractérisés par le fait que R1 désigne un radical alkyle ramifié saturé ayant de 3 à 20 atomes de carbone, et de préférence de 3 à 10 atomes de carbone, et que $R_3$ et $R_4$, indépendamment l'un de l'autre, désignent un radical alkyle linéaire comprenant de 2 à 12 atomes de carbone, et de préférence de 2 à 10 atomes de carbone.

17. Composés selon l'une des revendications 15 ou 16, caractérisés par le fait qu'ils sont choisis dans le groupe formé par :
- le N-néopentanoyl-2-octyl-dodécylamine,
- le N-néopentanoyl-2-butyl-octylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-octyl-dodécylamine,
- le N-(3,5,5-triméthyl-hexanoyl)-2-butyl-octylamine.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 98/01077

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/05 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DE 30 09 543 A (HENKEL) 24 September 1981<br>see claim 1; examples C,L<br>--- | 15 |
| X | CHEMICAL ABSTRACTS, vol. 123, no. 2,<br>10 July 1995<br>Columbus, Ohio, US;<br>abstract no. 19050w,<br>J.S. PRESTON ET AL: "Solvent extraction of uranium(VI) and thorium(IV) from nitrate media by carboxylic acid amides"<br>page 719;<br>XP002056530<br>see abstract<br>& SOLVENT EXTR. ION EXCH.,<br>vol. 13, no. 3, 1995, pages 391-413,<br>see the compound CN: 163930-78-7<br>---<br>-/-- | 15 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 September 1998 | 22/09/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Voyiazoglou, D |

Form PCT/ISA/210 (second sheet) (July 1992)

INTER[redacted]IONAL SEARCH REPORT

Int[redacted]Application No
PCT/FR 98/01077

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | M. BENOIT-GUYOD ET AL: "Recherches dans la série dipropylacétique VIII.-Structures homologues : amides et urées de la propyl-2-pentylamine" CHIMIE THÉRAPEUTIQUE, vol. 7, no. 5, 1972, pages 393-398, XP002056529 see example 179 --- | 15 |
| X | CHEMICAL ABSTRACTS, vol. 125, no. 19, 4 November 1996 Columbus, Ohio, US; abstract no. 247066c, T. DAGNAC ET AL: "A methodological approach to N,N-dialkylamide thermal degradation at low temperatures" page 1075; XP002056531 see abstract & J. ANAL. APPL. PYROLYSIS, vol. 37, no. 1, 1996, pages 33-47, see the compound CN: 182012-67-5 --- | 15 |
| A | WO 94 18940 A (ESTEE LAUDER) 1 September 1994 cited in the application see claims 1,5,21 --- | 1 |
| A | GB 2 001 083 A (IMPERIAL CHEMICAL INDUSTRIES) 24 January 1979 see claims 1,2,13 --- | 1 |
| A | US 5 476 643 A (A. W. FOGEL) 19 December 1995 cited in the application see claim 1 ----- | 14 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FR 98/01077

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|---|
| DE 3009543 | A | 24-09-1981 | NONE | | |
| WO 9418940 | A | 01-09-1994 | AU | 6442794 A | 14-09-1994 |
| | | | CA | 2156931 A | 01-09-1994 |
| | | | EP | 0686025 A | 13-12-1995 |
| | | | JP | 8507081 T | 30-07-1996 |
| | | | US | 5468471 A | 21-11-1995 |
| GB 2001083 | A | 24-01-1979 | AU | 518818 B | 22-10-1981 |
| | | | AU | 3780278 A | 10-01-1980 |
| | | | BE | 868890 A | 10-01-1979 |
| | | | CA | 1117689 A | 02-02-1982 |
| | | | CH | 640150 A | 30-12-1983 |
| | | | DE | 2830860 A | 01-02-1979 |
| | | | DK | 317278 A,B, | 16-01-1979 |
| | | | FR | 2397226 A | 09-02-1979 |
| | | | JP | 1570685 C | 25-07-1990 |
| | | | JP | 54037082 A | 19-03-1979 |
| | | | JP | 63030057 B | 16-06-1988 |
| | | | NL | 7807584 A,C | 17-01-1979 |
| | | | US | 4224212 A | 23-09-1980 |
| US 5476643 | A | 19-12-1995 | NONE | | |

# RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No
PCT/FR 98/01077

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 C07C233/05 A61K7/48

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 C07C A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

| Catégorie * | Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents | no. des revendications visées |
|---|---|---|
| X | DE 30 09 543 A (HENKEL) 24 septembre 1981<br>voir revendication 1; exemples C,L<br>--- | 15 |
| X | CHEMICAL ABSTRACTS, vol. 123, no. 2,<br>10 juillet 1995<br>Columbus, Ohio, US;<br>abstract no. 19050w,<br>J.S. PRESTON ET AL: "Solvent extraction of uranium(VI) and thorium(IV) from nitrate media by carboxylic acid amides"<br>page 719;<br>XP002056530<br>voir abrégé<br>& SOLVENT EXTR. ION EXCH.,<br>vol. 13, no. 3, 1995, pages 391-413,<br>composé du CN:163930-78-7<br>---<br>-/-- | 15 |

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

| Date à laquelle la recherche internationale a été effectivement achevée | Date d'expédition du présent rapport de recherche internationale |
|---|---|
| 9 septembre 1998 | 22/09/1998 |

| Nom et adresse postale de l'administration chargée de la recherche internationale | Fonctionnaire autorisé |
|---|---|
| Office Européen des Brevets, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Voyiazoglou, D |

1

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

| Catégorie ° | Identification des documents cités, avec,le cas échéant, l'indicationdes passages pertinents | no. des revendications visées |
|---|---|---|
| X | M. BENOIT-GUYOD ET AL: "Recherches dans la série dipropylacétique VIII.-Structures homologues : amides et urées de la propyl-2-pentylamine" CHIMIE THÉRAPEUTIQUE, vol. 7, no. 5, 1972, pages 393-398, XP002056529 voir exemple 179 --- | 15 |
| X | CHEMICAL ABSTRACTS, vol. 125, no. 19, 4 novembre 1996 Columbus, Ohio, US; abstract no. 247066c, T. DAGNAC ET AL: "A methodological approach to N,N-dialkylamide thermal degradation at low temperatures" page 1075; XP002056531 voir abrégé & J. ANAL. APPL. PYROLYSIS, vol. 37, no. 1, 1996, pages 33-47, composé du CN:182012-67-5 --- | 15 |
| A | WO 94 18940 A (ESTEE LAUDER) 1 septembre 1994 cité dans la demande voir revendications 1,5,21 --- | 1 |
| A | GB 2 001 083 A (IMPERIAL CHEMICAL INDUSTRIES) 24 janvier 1979 voir revendications 1,2,13 --- | 1 |
| A | US 5 476 643 A (A. W. FOGEL) 19 décembre 1995 cité dans la demande voir revendication 1 ----- | 14 |

1

# RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande internationale No
PCT/FR 98/01077

| Document brevet cité au rapport de recherche | Date de publication | Membre(s) de la famille de brevet(s) | Date de publication |
|---|---|---|---|
| DE 3009543 A | 24-09-1981 | AUCUN | |
| WO 9418940 A | 01-09-1994 | AU 6442794 A | 14-09-1994 |
| | | CA 2156931 A | 01-09-1994 |
| | | EP 0686025 A | 13-12-1995 |
| | | JP 8507081 T | 30-07-1996 |
| | | US 5468471 A | 21-11-1995 |
| GB 2001083 A | 24-01-1979 | AU 518818 B | 22-10-1981 |
| | | AU 3780278 A | 10-01-1980 |
| | | BE 868890 A | 10-01-1979 |
| | | CA 1117689 A | 02-02-1982 |
| | | CH 640150 A | 30-12-1983 |
| | | DE 2830860 A | 01-02-1979 |
| | | DK 317278 A,B, | 16-01-1979 |
| | | FR 2397226 A | 09-02-1979 |
| | | JP 1570685 C | 25-07-1990 |
| | | JP 54037082 A | 19-03-1979 |
| | | JP 63030057 B | 16-06-1988 |
| | | NL 7807584 A,C | 17-01-1979 |
| | | US 4224212 A | 23-09-1980 |
| US 5476643 A | 19-12-1995 | AUCUN | |